DETECTION OF TUBERCULOSIS IN PLWHA, A STUDY OF YIELD BY CB-NAAT AND MICROSCOPY WITH CD4 CO RELATION

Dissertation submitted to

The Tamil Nadu Dr. M.G.R. Medical University

In partial fulfillment of the regulations for

The award of the degree of

M.D. General Medicine [Branch- 1],

K.A.P.VISWANATHAM GOVERNMENT MEDICAL COLLEGE

& M.G.M.GOVERNMENT HOSPITAL,

TIRUCHIRAPPALLI.

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI

APRIL 2017

CERTIFICATE

This is to certify that the dissertation entitled **"DETECTION OF TUBERCULOSIS IN PLWHA, A STUDY OF YIELD BY CB-NAAT AND MICROSCOPY WITH CD4 CO RELATION"** is a bonafide original work of **Dr.K.SMITHA CHANDRAN** in partial fulfillment of the requirements of M.D General Medicine [Branch- 1] examination of THE TAMILNADU Dr. M. G. R. MEDICAL UNIVERSITY to be held in April 2017.

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ACKNOWLEDGEMENT

I wish to express my heartfelt and sincere gratitude to our DEAN **Prof. Dr. S. MARY LILLY, M. D.**, for allowing me to utilize the clinical material for this study I am extremely grateful to **Prof. Dr. N.K. SENTHIL NATHAN, M.D.,** Professor and Head of the Department, **Prof. Dr. S.KASIPANDYAN, M.D.,** Department of Internal medicine, K.A.P.V. Government Medical College and M.G.M.Govt. Hospital for permitting me to carry out this study and for his constant encouragement and guidance.

I whole heartedly thank Prof. **Dr. S. DHANAPAUL M.D., Professor** & **H.O.D**, Department of Microbiology, for his constant motivation and valuable guidance throughout my dissertation work.

I sincerely thank our registrar **Dr. RAJASEKHAR., M.D.,** for his continuous support and guidance.

I express my sincere gratitude to **Dr. V. P. ARIVUDAINAMBI, M.D., Dr. P. MAHALAKSMI, D.T.C.D.,** Assistant Professors of Thoracic Medicine and **Dr.S.M.MANIVANNAN, A.R.T M.O.,** for guidance and help during this study

I thank my unit Assistant Professors **Dr. RAJA MAHENDRA, M.D., Dr. M RAMESH, M.D.,** for their continuous motivation and valuable guidance throughout my work. I whole heartedly thank my parents, colleagues, friends and staff of our hospital for their support for this work.

I owe my sincere thanks to the Laboratory Services in K.A.P.V. Government Medical College and all the patients for their kind cooperation throughout the study.

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INTRODUCTION

1.1 BACKGROUND

Tuberculosis related deaths are rising in the world in an alarming trend. No wonder that this chronic infection is setting the major brakes in human resources and economy of a nation particularly the developing ones. Also the mortality in HIV due to TB is increasing and reported 36 million deaths worldwide in 2013.

The main reasons for this high mortality are because of lack of proper diagnosis in the apt time. This is particularly important in patients with HIV and TB co infection and extra pulmonary TB in special because the detection rates are low.(5,6) There is an urgent need to implement newer diagnostic modalities for detection of TB especially in highly HIV prevalent areas.

The diagnostic gold standard for tuberculosis detection is culture. But it takes longer time and cannot be relied for the implementation of immediate active treatment when compared to microscopy, especially with the Fluorescent LED microscopy which is a quick method of identification.(12,16)

For the detection of TB using microscopy, the sensitivity is an issue and that’s addressed partly by the implementation of CB NAAT in 2010 by WHO in HIV patients for the detection of TB.

In this study we are analyzing the role of LED microscopy and CBNAAT in detection of patients suspecting pulmonary and extra pulmonary TB in HIV positive patients and HIV negative patients.

Recent years witnessed rapid advances in embracement of newer technologies in the field of diagnosis of tuberculosis as well as the detection of drug resistant PTB. The Xpert MTB/RIF assay, which enables detection of Mycobacterium Tuberculosis(MTB) and Rifampicin (RIF) resistance was endorsed by WHO in December 2010. This test was specifically recommended for the initial diagnostic test for suspected drug-resistant and HIV-associated pulmonary tuberculosis.

Accurate point of care diagnostic test should be the one or a combination of some, which are affordable to the nation as well as able to detect the burden of tuberculosis with good sensitivity and specificity without compromising the time delay in diagnosis and hence treatment. Here the main comparison is between the LED fluorescence microscopy technique and CB NAAT.

1.2 AIMS AND OBJECTIVES

1. To compare the yield of detection of Pulmonary and Extra Pulmonary Tuberculosis inZeil Neilson smear negative patients with HIV infection by CBNAAT and fluorescent LED microscopy.

2. To compare the detection of pulmonary and extra pulmonary tuberculosis by LED fluorescent microscopy and CBNAAT in HIV negative patients.
3. To assess the difference in HIV positive patients and HIV negative patients of tuberculosis with CBNAAT and fluorescent LED microscopy.
4. To determine if there is any CD4 count co relation among PLWHA in terms of detection with these two techniques.

1.3 INCLUSION CRITERIA

1. PLWHA suspecting pulmonary TB with negative ZN smear test, positive chest X-ray findings.
2. PLWHA suspected with tuberculous lymphadenitis , tuberculous pleural effusion with negative ZN smear test.
3. HIV negative patients suspecting pulmonary TB, lymph node TB, or tuberculous pleural effusion with negative ZN smear test.

1.4 EXCLUSION CRITERIA

1. Patients suspecting pulmonary TB with normal chest X-ray
2. Patients in whom ZN smear test was positive
3. Patients with past history of TB, already taken ATT
4. All diabetes mellitus patients.

CHAPTER -II

MATERIALS AND METHODS

This study was conducted in K.A.P.V Govt. Medical College, Trichy, January2015-April 2016. The patients who were suspecting tuberculosis were selected from HIV positive patients and HIV negative patients. Patients with pulmonary symptoms of cough of more than 1 week with weight loss or loss of appetite, night sweats etc. were subjected to chest X-ray and those with chest x-ray findings suggestive of tuberculosis or consolidation were selected for the study. Also the patients with these symptoms and pleural effusion or lymph node positivity were also selected. All diabetes mellitus patients were excluded from the study.

Based on these 40 patients suspecting pulmonary TB were selected with chest X-ray findings. Two early morning sputum samples were sent to microbiology laboratory in sterile containers. These were subjected to examination for AFB using Zeil Neelson staining and detection with LIGHT MICROSCOPY,FLUORESCENT LED MICROSCOPY and also CB NAAT technique for nucleic acid amplification and identification of MTB.

Smears for LED fluorescent microscopy were prepared following standard procedures of preparation of slides, and staining with Auramine .All specimens were concentrated by cytocentrifugation. All smears reported as “scanty” acid-fast bacilli (AFB) by LED fluorescent microscopy were considered as positive results for performing the analysis of the study. Sample

preparation and Xpert MTB/RIF procedure were performed by trained operators as described previously [2,17].Statistical analysis was performed using SPSS software, version 20.

The study was approved by the Ethical Committee of the K.A.P.V Govt. Medical College, Trichy Institutional Review Board.

The results were given as AFB negative,1+,2+,3+,4+ and CB NAAT negative, high, medium, low, very low. All ZN smear test positive patients were excluded from the study.

Similarly, the matted lymph nodes were subjected to FNAC and send for analysis using these 2 methods, also 10 patients of suspected tuberculous pleural effusion were selected and pleural fluid were send for analysis with LED fluorescent microscopy and CB NAAT and results were analyzed.

CD4 count of all the patients with HIV positivity were noted at the time of detection of tuberculosis and analyzed if it has any co relation with these results. Results were analyzed statistically with SPSS software, version 20.

CHAPTER - III

REVIEW OF LITERATURE

Tuberculosis is an age old infection caused by Mycobacterium Tuberculosis complex. It is thought to be emerged 70,000 years back in Africa, and expanded to modern worlds then onwards.(8).This disease most commonly affects the lungs in two third of the patient, but involves almost all of the organ systems in body and the systems other than lungs are involved in one third of the patients.

The public health importance of this disease is that when it is drug susceptible and treated properly, curable in majority of patients and if left untreated fatal in 50-60% of patients within 5 years.(8)

3.1 EPIDEMIOLOGY

In 2013, 5.7 million new TB cases were reported worldwide to WHO. Out of which 95 percent was from the developing countries. But this is considered as around 2/3rd of total new cases as the infections are under diagnosed in the developing countries because of poor resources in detection as well as socio economic, cultural reasons prevailing mostly in the developing countries. . Based on this, the estimated total new TB cases worldwide by WHO 2013 was 9 million.

Of the newly diagnosed total TB cases by WHO in 2013, 13% were HIV associated. And the mortality was also high in this group of patients. A total of 0.36 million out of Out of 1.49 million new patients 0.36 million patients were died in 2013 because of tuberculosis.(8).

Coming to the matter of drug resistance, about 28% of the total cases of tuberculosis were drug resistant.

3.2 ETIOLOGICAL AGENT

Mycobacterium Tuberculosis, is a spore forming and rod shaped bacteria, 0.5-3-micronlength. This is a gram negative, but acid fast positive bacteria because of high content of mycolic acids, other long chain fatty acids and lipids.

Some other microorganisms also display some acid fastness. These include species of Noccardia, Rhodococcus, Legionella micdadei, and the protozoa Isospora & Cryptosporidium. In the cell wall of mycobacteria, lipids like mycolic acids are linked to underlying arabinogalactan and peptidoglycan molecules. Because of this particular structure, there is very low permeability of the cell wall to the anti-bacterial agents.

Yet another molecule in the cell wall of mycobacteria, lipoarabinomannan, is involved in the interaction between bacteria and host cells, resulting in the increased survival of Mycobacterium tuberculosis inside the macrophages.

The genome sequence of Mycobacterium tuberculosis consists of 4043 genes encoding 3993 proteins and fifty genes encoding RNAs. There is a high guanine and cytosine concentration (65.5%). This indicates the aerobic lifestyle of organism. This explains the upper lobe preference in pulmonary tuberculosis. A large proportion of genes are devoted to the production of enzymes involved in cell wall metabolism.

3.3 MODE OF TRANSMISSION

The transmission of infection is via aerosolized particles from respiratory tract when the patient coughs. These particles are less than 5-10 microns in diameter. These remain suspended in the atmosphere for several hours, and there are approximately 3000 such particles in one cough. On an average, a person may transmit infection to 20 contacts before being recognized as a patient. Transmission through skin or placenta are uncommon and not of much significance.

3.4 RISK FACTORS FOR ACTIVE ILLNESS

1. Recent infection with Mycobacterium tuberculosis
2. Fibrotic lesions, silicosis.
3. HIV co-infection
4. CKD on dialysis
5. Diabetes mellitus
6. Smoking

7. IV drug abuse, immune suppressive treatment
8. Malnutrition and underweight.

Among these the highest odd's ratio is for HIV infection.

The relation with age is that, the adolescent and early adulthood age groups are particularly more prone for active infection because of unknown reasons. In female, clusters in 25-34 years of age and there is a rise of active disease in elderly because of waning immunity.

3.5 NATURAL HISTORY

- One third of PTB died within 1 year(8)
- More than 50% died within 5 years
- 5-year mortality rate among sputum positive PTB 65%

3.6 PATHOGENESIS AND IMMUNITY(9)

The infection with Mycobacterium tuberculosis begins with the inhalation of droplet nuclei containing large amount of mycobacteria, released when an infectious patients coughs and when they are taken up by inhalation by a close by stander... The majority of inhaled bacteria are trapped in the upper airway tract and are expelled by ciliated mucosal cells. But a small fraction (usually less than10%) will reach the alveoli. Alveoli have a unique immunoregulatory environment. The pulmonary alveolar macrophages, which are the key immunoregulatory cell in alveoli, have not yet been activated to phagocytose the bacteria.

The adhesion of TB mycobacteria to macrophages results from binding of the bacterial cell wall to a large variety of cell-surface molecules expressed over the macrophages, including complement receptors, the mannose receptor, the immunoglobulin receptors, and some scavenger receptors.

The complement activation enhances the phagocytosis. After phagocytosis, TB bacteria will get captured into the lysosomes to form endosomes. They will cause endosomal manipulations, i.e. maturation arrest, lack of acid pH and ineffective phagolysosome formation. Because of these, they multiply inside the phagosomes such as phagosome lysosome fusion and inflammatory cytokine production.

After phagosome formation, the survival of Mycobacterium Tuberculosis seems to be dependend on reduced acidification. This results in a lack of assembly of a complete vesicular proton adenosine triphosphates.

A series of complex events are generated by the bacterial cell wall lipoglycanlipoarabinomannan (ManLAM). This inhibits the intracellular release of calcium. By this the Calcium Calmodulin pathway is impaired, and the TB bacteria survive within the phagosomes.

The phagosome is found to inhibit the production of phosphatidyl inositol 3 phosphate (PIP3). PIP3 causes membrane maturation and sorting in phagosomes, thereby the phagolysosome formation which would destroy the bacteria. If the bacilli successfully in arrest phagosome maturation, then the replication begins. Eventually the macrophage ruptures and releases its bacillary contents. Other uninfected macrophages are then recruited and the

infection cycle continues, ingesting dying macrophages and their bacillary content, thus in turn becoming infected themselves and expanding the infection.

After 3 weeks of initial infection, processed TB bacterial antigens reach the draining lymph nodes, and are presented by dendritic cells via MHCII to CD4 T cells. The IL 12 secreted by macrophages causes proliferation of CD4 T cells of Th-1 variety, and they secrete IFN-Gamma.

Interferon gamma causes macrophage activation-TNF secretion. Monocyte differentiation to epithelioid histolytic and granulomatous reaction. Also iNOS is activated, NO acts as powerful oxidizer and release of reactive free radicals Nitrogen and Oxygen species.

3.7 CLINICAL MANIFESTATIONS

Pulmonary TB manifestations are broadly divided as pulmonary and extra pulmonary. Pulmonary tuberculous diseases are categorized as primary and post primary. Primary TB occurs after the initial infection, affects mainly children, infectivity is low, cavitations and permanent sequale are rare and affects middle and lower lung zones.

Post primary/adult type affects mostly the apical and posterior segments, and runs a chronic debilitating course.

Extra pulmonary TB mostly manifests in lymph nodes, pleura, genital and urinary tract, joints and bones, meninges, peritoneum and pericardium.

Lymph node disease manifest as painless matted nodes mostly in posterior cervical region. Associated pulmonary tuberculosis is present in less than 50% of patients. Lymph node tuberculosis is particularly frequent among children and HIV infected patients. Earlier, the tuberculous lymphadenitis was mostly caused by Mycobacterium bovid, but now its caused mostly by Mycobacterium tuberculosis.

The most common sites for tuberculous lymphadenopathy is posterior cervical group and supraclavicular groups. The painless swelling of lymph nodes in these regions were historically referred as scrofula.

In early disease lymph nodes are discrete and over the time they progress to matted nodes. On passage of time, they may develop fistulous tracts with discharge of caseous material. The systemic symptoms are usually uncommon, but present in HIV individuals

The diagnosis in tuberculous lymphadenopaphy can be established by fine-needle aspiration biopsy(FNAB) or surgical excision biopsy. The yield by fine needle aspiration is around 80 %, detection and with culture also yields around 90%,

Lymph node involvement in HIV-TB, they have less organized granulomas, so more chance of detection by microscopy and culture.

20% of patients, there is pleural involvement. It’s mostly due to hypersensitivity reactions to the TB microbial antigens or sometimes contiguous spread. Associated parenchymal lesions are seen in less than one third of patients. Pleural fluid CB NAAT is not generally recommended

because of low sensitivity. Pleural biopsy is the preferred method of investigation.

Isolated pleural effusions are usually due to primary infection and hypersensitivity reaction to mycobacterial antigens. Post primary infections may result in contiguous spread if pleurisy is present.

Depending up on the extent of reactivation, the effusion can be small, and resolve spontaneously. It may be sometimes large to cause symptoms like fever, pleuritic chest pain, and breathlessness. Physical examination reveals dullness to percussion and absence of breath sounds. A chest X ray reveals the effusion. In about one-third of cases, shows a parenchymal lesion.

Pleural fluid aspiration and analysis is essential for reaching the diagnosis. Mostly the fluid is straw colored, and sometimes hemorrhagic. The nature of fluid is exudative with protein concentration of more than 50% of in serum. There will be normal to low concentration of glucose. pH will be normal to acidic, around 7.3. Total leukocyte count is usually 500–6000/μL). In early stages neutrophils are predominant, and in late stages lymphocytes are more predominant.

AFB are rarely seen on smear, and cultures often may be false negative sometimes. Determination of adenosinedeaminase (ADA) in pleural fluid may be a useful screening test. If the value is too low TB may be excluded.

Measurement of IFN-γ can be helpful. These are done either directly or through stimulation of T cells sensitized with mycobacterial antigens. Pleural

biopsy is recommended over pleural fluid it reveals granulomas and/or yields a positive culture

Genito urinary TB accounts for 10-15% of total tuberculous patients, and 75% will be having pulmonary involvement. Local symptoms like nocturnal, dysuria, frequency predominates. Routine urine investigations reveal pyuria, hematuria, and culture negative UTI. Lower urinary tract TB can progress to pyelonephritis, in kidneys etc. Genital TB is more common in females and affects fallopian tubes, endometrium more commonly resulting in infertility and abnormal menstrual bleeds. In males mostly present as epididimoorchids, Bones and joints tuberculosis is about 10%.

CNS involvement is for about 5% of patients. Usually in younger age group's culture is the gold standard, detects up to 80%, but CB-NAAT also has a similar detection rate.

Gastrointestinal TB is rare-3.5%. It more commonly involves terminal ileum and cecum and peritoneum. In TB peritonitis, yield by direct smear and culture of fluid is low. Peritoneal biopsy should be considered for detection.

3.8 HIV ASSOCIATED TUBERCULOSIS

Tuberculosis is the most common disease affecting HIV patients. Certain data highlighting the role of importance of HIV TB co infections are given below.(8)

- Tuberculosis is responsible for about 24% of all-cause mortality in HIV patients.

- In patients positive for Tuberculin sensitivity test (TST), the annual risk for tuberculosis is 3-13%.
- Evolution of active tuberculosis is faster in patients with HIV, rather in a few weeks as opposed to months to years in general population.
- When Cell mediated immunity(CMI) is only partly affected, pulmonary TB is manifested as in immune patients, that is with infiltrates and cavities and less lymph node enlargements, where as if severely affected, there will be diffuse infiltrates without cavitation is seen and there will be more lymph node enlargements, the disease more or less resembles primary tuberculosis.
- Sputum smears are less frequently positive among HIV-TB co infections, so that there is a diagnostic challenge for these patients.
- Incidence of extra pulmonary tuberculosis is higher than the normal population, constituting about 40-60% of the cases.
- It is now recommended that the Xpert MTB/RIF assay should be used for the diagnosis of TB in HIV, not the microscopy and treatment should not be delayed if Expert MTB/RIF assay is positive. But culture is the gold standard test.
- Yet another important consideration is the Immune reconstitution inflammatory syndrome (IRIS). This occurs in the HIV-TB co infected patients if we are starting ART first because of undiagnosed TB. When effective ART is implemented, cell mediated immunity of the patient improves and there is a large cytokine release to the tubercle bacilli,

which will cause flare-up of symptoms and signs like lymphadenopathy, respiratory symptoms or chest X raymanifestations. Lower baseline CD4 count and earlier starting of ART are the main risk factors. This is one of the reason why we have to rely upon a method of higher diagnostic yield to detect TB in HIV rather than the conventional methods.

- HIV patients with culture positive or AFB positive TB may present with normal chest radiograph. The XpertMTB/RIF assay, CBNAAT assay is the rapid diagnostic test then. There is a sensitivity of around 60% among AFB-negative culture-positive cases and 97% among AFB-positive cases.

3.9 WHOM TO TEST?

How the TB diagnosis should take place in India is guided by the standard tests by Revised National Tuberculosis Control of India (RNTCP). These standards were published in 2014 and describe the tests and protocol for the diagnosis of tuberculosis for all those patients who are suspected of tuberculosis including the special categories, like as those with tuberculosis and HIV co infection.

Any person who has signs and symptoms suggestive of tuberculosis including

- cough for more than 2 weeks
- fever for more than 2 weeks
- significant weight loss, loss of appetite
- hemoptysis

- abnormality in chest x-ray with respiratory symptoms
- Household contacts of pulmonary TB with respiratory symptoms.

3.10 WHOM TO SCREEN?

- People living with HIV (PLHIV/PLWHA)
- people who are malnourished
- People who have diabetes or cancer
- People on steroid therapy
- People on immune suppressive therapy.

These populations should be regularly screened for signs and symptoms suggestive of tuberculosis.

3.11 WHAT IS ENHANCED CASE FINDING?

Having a high level of suspicion for tuberculosis in all medical encounters and then identifying or excluding tuberculosis using a combination of clinical questionnaires, radio graphical and simple microbiological testing.

Enhanced case finding should be undertaken in certain high risk population groups like

- healthcare workers
- prisoners
- slum dwellers
- certain occupational groups such as mineworkers
- Laboratory workers

3.12 DIAGNOSIS OF TUBERCULOSIS

1. AFB MICROSCOPY
2. NUCLEIC ACID AMPLIFICATION TECHNOLOGY
3. MYCOBACTERIAL CULTURE
4. RADIOGRAPHIC PROCEDURES
5. DRUG SUSCEPTIBILITY TESTING
6. ADDITIONAL DIAGNOSTIC PROCEDURES

3.12.1. AFB MICROSCOPY

The most reliable single method in diagnosis of Tuberculosis is sputum microscopy. Direct or concentrated smears are used normally. Its recommended to use new slides for every use, i.e. the slides should never be reused. It should be prepared from thick purulent part of sputum. They are dried and heat fixed and stained, to be examined under microscope.

Zeihl-Neelson staining or fluorescent staining is used. If ZN staining, it’s viewed under oil immersion objective, under light microscope, the bacteria are seen as bright red rods.

A minimum of 10,000 bacilli should be present in 1 milliliter of sputum for ready diagnosis by smear. To give a negative report, a minimum of 300 fields should be examined. And a positive report is given if at least two typical bacilli are demonstrated.

Typical bacilli mean appearing barred or beaded, since saprophytes are stained uniformly.

TABLE 1: ZN SMEAR EVALUATION AND AFB REPORT

NO. OF AFB	NO OF FIELDS	REPORT
0	300	NOT SEEN/NEGATIVE
1-2	300	DOUBTFUL/REPEAT
1-9	100	1+
1-9	10	2+
1-9	1	3+
10 OR MORE	1	4+

When large number of smears is diagnosed daily, fluorescent microscopy is better. The smears are stained with fluorescent stains and visualized under ultra violet illumination, and appear as bright rods in contrast to a dark background.LED microscopes are also available which are cheaper, and are as good as traditional fluorescent microscopes in sensitivity.

ADVANTAGE OF MICROSCOPY

- Cheap(3)
- Maintenance cost is low

DISADVANTAGES

- Time consuming
- Inter observable variation
- Less sensitive(3), poor positive predictive value.(3)
- Saprophytes can be mistaken for true positives
- Biosafety issues
- Not much suitable for specimens other than sputum
- HIV-TB confection, smear deviation rate is low

3.12.2. NUCLEIC ACID AMPLIFICATION TECHNIQUES (8)

This is based on the amplification of nucleic acids of the Mycobacterium Tuberculosis, so that, the specificity is high.

ADVANTAGES

- Less time consuming
- Detection and Rifampicin resistance identified within 2-3 hours.
- Minimal biosafety and training requirements.(7)
- Sensitivity of 98% in AFB positive and 70% in AFB negative.
- Can be housed in non-conventional laboratory settings(7)

DISADVANTAGES

- Cost effectively
- Maintenance charges are relatively higher.

The current WHO recommendation (14) is to use the nucleic acid amplification test as the initial diagnostic test in

- suspected MDR-TB adults and pediatrics
- HIV-associated TB.
- If resources available as a follow up test to smear positive TB
- CSF from suspected TB meningitis
- No respiratory specimens like gastric lavage, FNAC specimens, pleural biopsies etc. This test has a sensitivity of 98%

3.12.3 CULTURE OF MYCOBACTERIA

Definitive diagnosis of tuberculosis is based on culture or nucleic acid amplification. Specimens are cultured on egg or agar medium (e.g. Löwenstein – Jensen (LJ) or Middlebrook) and incubated at 37°C. As the Mycobacteria are slow growers, 4–8 weeks are required for growth to be detected. M. tuberculosis is identified presumptively with growth time, pigmentation of colony, morphology and biochemical tests for speciating the isolates. In well-equipped laboratories; liquid culture and molecular methods HPLC for isolation and species identification instead of solid culture and the biochemical tests.

Fluorescent growth indicator tubes are available for the rapid identification of growth now a day. Immunochromatographic low cost antigen detection is also aiding in species identification. All these methods have limited the time needed for culture identification to be reduced to about 2-3 weeks.

So other main disadvantages are

- Requirement of sophisticated laboratory
- Cost
- Time Consumption

ADVANTAGES

- gold standard for diagnosis
- drug sensitivity possible simultaneously

3.12.4 DRUG SUSCEPTIBILITY TESTING

1. Direct on liquid medium-3 weeks
2. Indirectly with culture isolates on solid or liquid media –about 8 weeks.
3. Xpert MTB/RIF assay detects Rifampin resistance
4. Molecular line probe assays is available now for INH and Rifampicin
5. Microscopically observed drug susceptibility(MODS)-noncommercial, cheap
6. Nitrate reductase assays -useful in resource poor scenarios

3.12.5 RADIOLOGICAL DIAGNOSIS

The initial suspicion of PTB is based on chest X-ray PA view. The classic picture is upper lobe disease with pulmonary infiltrates and cavities, but any radiographic pattern may be seen that is from normal film or solitary nodule or diffuse infiltrates are seen. In HIV-TB co infection, the chest X-ray

findings are not seen as the classical picture, more when the immunity is low. CT Chest is helpful with doubtful X-rays and Extra Pulmonary Tuberculosis like Pott's spine. MRI, is useful for TB meningitis.

3.12.6 SEROLOGICAL TESTS

They are based on antibody detection to Mycobacterial antigens, mostly used in developing countries. Disadvantages include:

- Not useful for diagnosis, especially with low probability of TB
- Low sensitivity and specificity
- Poor reproducibility(14)

WHO issued negative recommendation in 2011 for these tests even in resource poor settings(10). Determinations of ADA and IFN-γ in pleural fluids are considered as adjunctive tests in pleural TB, not recommended in other extra pulmonary tuberculosis.

3.12.7 RNTCP LABORATORY NETWORKS

A wide network of laboratories were established by RNTCP throughout India.TB tests can be done to diagnose people who have TB. These are primarily intended for

- Proper diagnosis of TB with good sensitivity and specificity.
- For the assessment and follow up of detected tuberculosis.
- For the timely detection of drug resistance in TB patients.

The laboratory system includes:

1. National Reference Laboratories or (NRLs)
2. State level Intermediate Reference Laboratories or (IRLs)
3. Culture & Drug Susceptibility Testing laboratories (C and DST laboratories)
4. Designated Microscopy Centers or (DMCs).

3.12.8 LED FLOURESCENT MICROSCOPY

In traditional light microscopy using ZN technique, each of the smear examination may take an average of 5-10 minutes. These put high workloads for laboratories, and may consequently result in decreased reliability.

Fluorescent microscopy (FM), was introduced as an alternative to light microscopy. The advantages over conventional microscopy includes,

- 10% more sensitive than ZN smear microscopy (12).
- Fluorescent acid fast bacilli (AFB) can be seen at lower magnification, so they can be examined in lesser time compared to light microscopy. The time reduction is about 25%.
- Can reduce the laboratory workloads.

But the disadvantages include high cost and complexity of system as it is using mercury vapour lamps. There is a need for a dark room, and also health risks to laboratory workers due to exposure of ultraviolet rays are yet another concern.

Because of these technical difficulties, illumination systems based on Light emitting diodes (LED) were implemented.

LED fluorescent microscopy holds several advantages over the conventional mercury vapour lamp fluorescent microscopy as well as the standard light microscopy.

- Relatively inexpensive.
- Have an effective lifespan of thousands of hours (13).
- Easily manageable in terms of power supply, that is it can work even with power supply from batteries.

Because of all these advantages LED fluorescent microscopy is more suitable for resource poor countries.

One important concern is with specificity. Some of the studies showed that, LED fluorescent microscopy has higher sensitivity but lower specificity than ZN smear microscopy when compared to the gold standard, culture of Mycobacteria.

3.13 XPERT MTB/RIF ASSAY/CBNAAT-IN AND OUT

The Xpert MTB/RIF assay is a cartridge based nucleic acid amplification test, which is an automated test that can identify MTB DNA and resistance to Rifampicin (RIF) by nucleic acid amplification test or NAAT. It was developed by the laboratory of Professor David Alland at the University of Medicine and Dentistry of New Jersey.(17).

In December 2010, the world health organization endorsed the Xpert MTB/RIF assay in TB endemic countries.(2,15).

Tuberculosis is still a deadly and fiery public health threat today, though it is considered as an age old disease developing along with mankind evolution.

Tuberculosis is mostly diagnosed by chest X-rays, the microscopy with special stains, the growth in culture and the Mantoux test. The smear microscopy test has some problems in HIV positive patients, children and also in patients with low bacterial load.

The Xpert MTB/RIF assay has high sensitivity & specificity for detection of pulmonary TB. An in vitro study demonstrated detection of as small as 131 colony forming units(cfu) per ml , compared to about 10,000 cfu with conventional smear microscopy.(4).

Susceptibility to drugs could only be diagnosed from the growth of MTB in culture which takes long time, about six weeks and needs high quality laboratories and cost.

Drug susceptibility testing is highly relevant because tuberculosis is becoming increasingly resistant to two of the major antiTB drugs, INH and Rifampicin, which is called MDR TB, and it needs longer time and special drugs to treat.

3.13.1 HOW IT WORKS?

The Xpert MTB/RIF assay purifies and concentrates Mycobacterium Bacilli from samples, isolates the genomic material from these captured

bacteria by sonication and then amplifies the genomic DNA by polymerase chain reaction (PCR).

This process also identifies all the clinically significant mutations in the RNA polymerase beta (rpoB) gene causing Rifampicin resistance in the Mycobacterium Tuberculosis genome in a real time process using fluorescent probes which are called the molecular beacons.

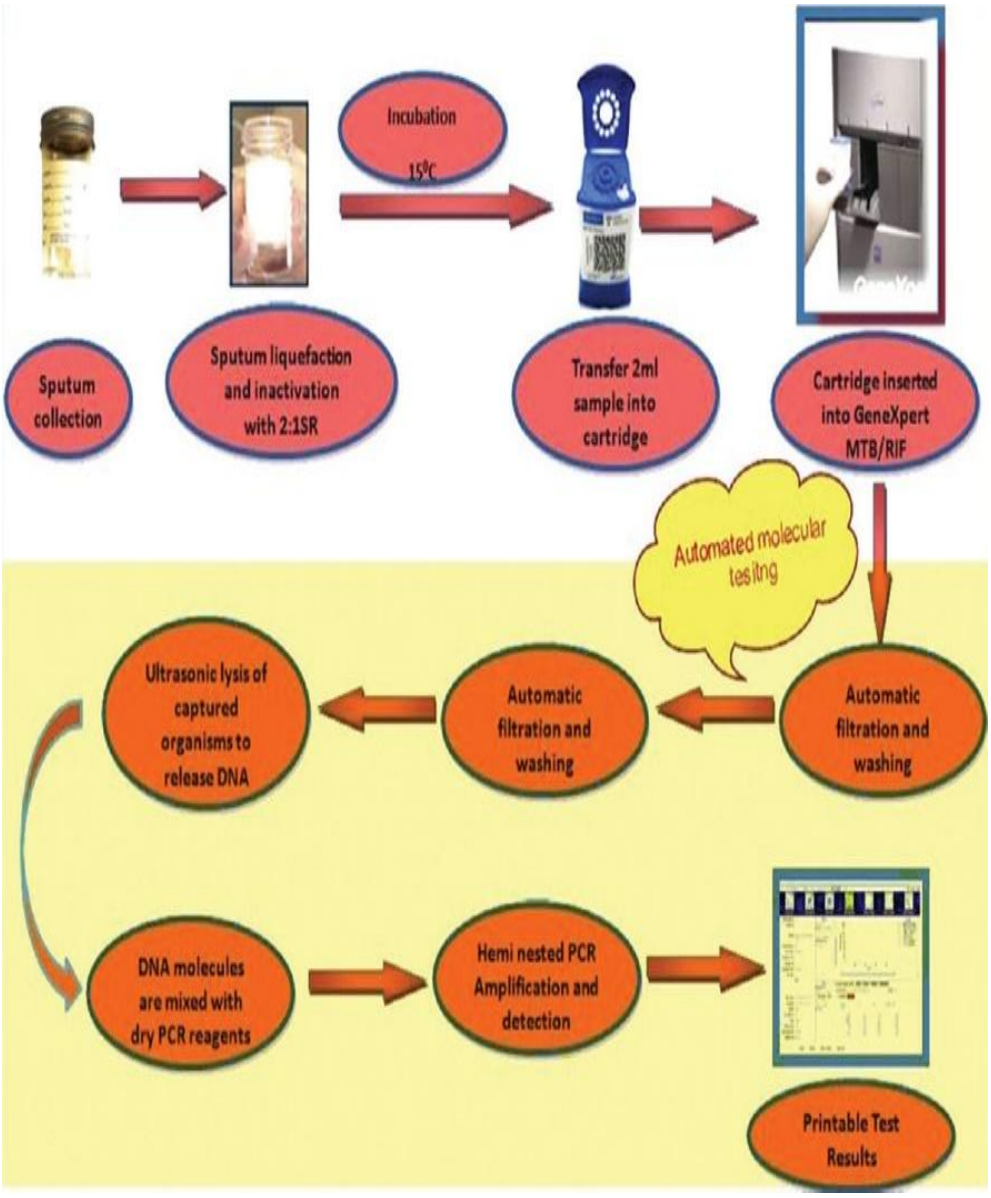
Results are obtained roughly in about 90 minutes, with minimum biohazard and a very little technical training for operation. This can even be set up easily in a simple laboratory without much technical requirements.

A review to assess the diagnostic accuracy of Xpert MTB/RIF assay, found that when its used as an initial test without smear microscopy it had a pooled sensitivity of 89% and a specificity of 99%.However, when it was used for cases of negative smear microscopy the sensitivity was only 67% and specificity 99%.(19)

In another clinical study, the sensitivity of the test on a single sputum sample was 92.2% for culture positive TB and 98.2% for both smear and culture positive patients and 72.5% for smear negative but culture positive cases, and there was a specificity of 99.2%. Sensitivity and specificity were slightly higher when three samples were tested.(5)

CBNAAT was adopted in India by RNTCP in 2012. It first started as a pilot project in Maharashtra state, India. CBNAAT is currently available at more centers and the aim is to establish a link with all the peripheral hospitals to medical college hospitals and also implemented in private set up.

In our K.A.P.V Govt. medical college Trichy, Tamil Nadu, India CB-NAAT started functioning since 2015 January.



3.13.2 A NOTE ON DRUG RESISTANCE IN TUBERCULLOSIS

Drug resistance usually occurs because of point mutations occurring in the genome of Mycobacterium Tuberculosis. The Rifampicin resistance is associated with rpob gene mutation in 95% of cases. The resistance to Isoniazid, the mutations are mainly in the katG (50–95%) and inhA (up to

45%) of genes. For Pyrazinamide resistance gene involved is the pncA gene (up to 98%) and to Ethambutol it is embB gene (50–65%). For the second line drugs, for Fluoroquinolones mutation is in the gyrA–gyrB genes (75–95%) and for Aminoglycosides mainly in the rrs gene (up to 80%).

Because of these different gene involvement, there is no cross resistance among the commonly used drugs. The development of drug resistance in Tuberculosis is almost invariably as a result of monotherapy. In addition, the usage substandard quality drugs also can cause drug resistant Tuberculosis. Yet another, but the most important factor is patient compliance to treatment which has to be ensured for the prevention of a dreadful global burden- the drug resistant Tuberculosis.

Drug resistant TB can be either primary or acquired. Primary drug resistance is that is present at the time of starting the treatment. Secondary drug resistance occurs during the treatment, that is initially patient will be responsive, but due to several afore mentioned reasons, resistance develops.

- MDR TB: Multi Drug Resistant TB- Resistant to both Isoniazid and Rifampicin
- XDR TB: Extremely drug resistant TB- MDR strains with drug resistance to any of Flouroquinolones and to any of the three second line injectables like Amikacin, Kanamycin ,Capreomycin.

3.14 HIV/AIDS, PATHOGENESIS AND RELATION WITH TUBERCULOSIS

HIV is the etiologic agent of AIDS, it belongs to Human Retrovirus family and the Lentivirus subfamily.

The hallmark of HIV and AIDS is a florid immunodeficiency resulting from a progressive both qualitative and quantitative deficiency of the subset of T lymphocytes, the helper cells. This occurs in setting of polyclonal immune system activation.

These Helper T cells are defined phenotypically by the presence of CD4 molecule on its surface, which serves primarily as the cellular receptor for HIV. The major coreceptors are CCR5 and CXCR4,for fusion and entry to cells, also serve as the primary receptors for chemo attractive cytokines known as chemokines.

The mechanisms responsible for cellular depletion and dysfunction of CD4 T cells include

1. Direct infection and destruction by virus.
2. Indirect effects like immune clearance, cell death associated with abnormal immune activation, immune exhaustion etc.

Approximately one third of all deaths in AIDS are associated with Tuberculosis and it is the primary cause of death in about 15% of patients with HIV. In India, prevalence is about 10% with HIV and active TB. Untreated TB will accelerate the course of HIV infection.

In contrast to infection with atypical mycobacteria, the active TB develops early in the course of HIV infection and can be considered as an early clinical sign of HIV disease. In one study, the median CD4 count at presentation of Tuberculosis was 326/µL.(8) The clinical manifestations of TBin HIV patients are quite varied and show difference in radiological presentation with difference in CD4.

Patients with relatively high CD4+ T cell counts, there will be typical pattern of pulmonary reactivation that is they present with fever, cough, difficulty in breathing, weight loss, evening rise of temperature, and a chest x-ray with upper lobe apical cavities.

In patients with lower CD4 T counts, disseminated diseases are more common and chest x-ray reveals diffuse or lower lobe bilateral infiltrates consistent with miliary spread, pleural effusions, or hilar prominence due to lymphadenopathy.

Some patients may have no symptoms, and screening for TB should be a part of the initial evaluation of all patients with HIV infection.

CHAPTER - IV

PREVIOUS STUDIES

1) An observational study Pulmonary Medicine Maharajah's Institute of Medical Sciences, Sowjanya et al, Vizianagaram 2012-2013. Out of 205 sputum samples from HIV status unspecified patients, 108(52.68%) were ZN AFB smear positive, 96 (47.32%) were negative. In CBNAAT,144 (70.24%) were MTB positive and 61 (29.76%) negative. All results were statistically significant. The test also detected 4 RIF-resistant specimens.(18).
2) In another study, by Gerardo et al, in Badalapalli RDT hospital, Andhrapradesh, in 2011-12, shows that the CBNAAT assay can increase more than three times the rapid diagnosis of Extra Pulmonary Tuberculosis in HIV positive patients compared to LED fluorescent microscopy.(7)
3) Tortolli and colleague's lab based study with eight nationally accredited laboratories in Italy. 268 of Extra Pulmonary Tuberculosis disease, compared with culture, the sensitivity and specificity of Xpert MTB/RIF assaywere 79.0% and 97.3% respectively.(20)
4) Ligthelm *et al* study showed excellent Xpert MTB/RIF assay sensitivity (96.7%) and specificity (86.6%) in patients with tuberculous lymphadenitis. (11)

5) Lawn and Zumla study showed a high sensitivity (81.3% for Extra Pulmonary Tuberculosis) of CBNAAT on a large number of non-respiratory samples.(10)

6) In another study, Boheme et al, conducted in patients from 5 sites in South Africa and Mumbai, India, patients suspecting pulmonary TB, HIV negative and positive were studied with sputum sample. The tests done were, AFB microscopy, ZN method, culture in LJ media and CBNAAT. Among culture positive PTB, the sensitivity of the CBNAAT was 97.6%. For smear and culture positive patients, the sensitivity was 99.8, smear negative culture positive, it was 90.2%.(5)

   The sensitivity with CBNAAT was compared between HIV positive(98.4%)and negative individuals(93.9%),but there were no statistically significant co relation.(5)

7) Study conducted by Avashiya et al in TB hospital Indore India from, Extra Pulmonary Tuberculosis lymphadenitis samples, cold abscess, CSF and pleural fluid were studied in HIV negative individuals.MTB was detected in 46 patients out of 81 (56.7%) pus samples, 24 of 103 (23.3%) pleural fluid aspirates, and 15 of 45 (33.3%)CSF samples. The analysis revealed CBNAAT has true diagnostic potential in Extra Pulmonary Tuberculosis with good sensitivity.(2)

CHAPTER - V

STATISTICS AND DISCUSSION

A total of 130 patients were selected for thesis study. Out of these 80 patients were suspected Pulmonary Tuberculosis patients, of which 40 were HIV positive and other 40 were HIV negative.

In rest of the patients, i.e. 50 patients was suspected Extra Pulmonary TB(EPTB) patients. Out of which 30 patients were suspected of tuberculous lymphadenitis and FNAC samples were taken from them. In this group also 15 were HIV positive and other 15 were HIV negative.

Out of 50 patients of Extra Pulmonary Tuberculosis, 20 patients were suspected of tuberculous pleural effusion and the sample taken was pleural fluid. Here also 10 were HIV positive and other 10 were HIV negative.

In each group, age, sex, BMI were analyzed for any co relation between HIV positive and negative patients.HIV positive patients were categorized as pre ART patients, and patients on ART. Duration also was noted in months in each group.

Age were categorized as 5 groups as less than 20yrs,20-30 years,30-40 years,40-50 years and more than 50 years.

5.1 PULMONARY TUBERCULOSIS

TABLE 2: CATEGORIZATION OF PTB SUSPECTING PATIENTS ACCORDING TO HIV STATUS

PTB SUSPECTING PATIENTS	NO.OF PATIENTS (n=80)	PERCENTAGE (100%)
HIV POSITIVE	40	50.0
HIV NEGATIVE	40	50.0

Out of 80 patients with suspicion of PTB selected for study,40 were HIV positive and 40 were HIV negative.

5.1 A: AGE DISTRIBUTION

Both these group of patients were stratified based on age groups into 5 categories. The distribution of age in these groups were graphically represented as:

CHART 1-AGE DISTRIBUTION: SUSPECTED PTB,HIV POSITIVE

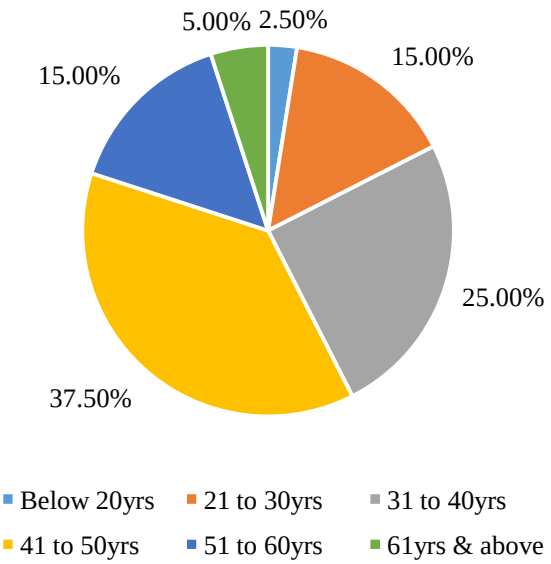
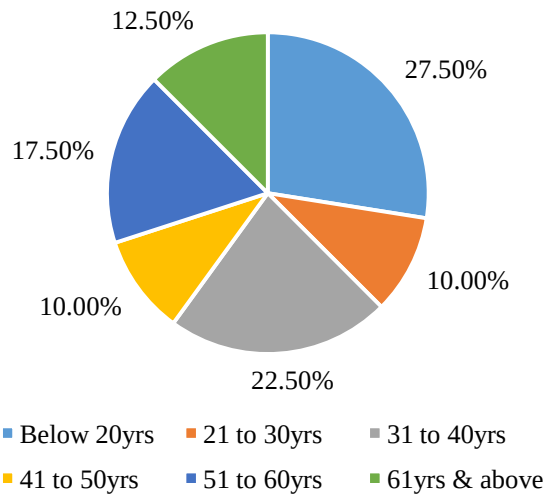


CHART 2 AGE DISTRIBUTION: SUSPECTED PTB,HIV NEGATIVE



When PTB suspecting HIV positive patients were stratified based on age, a majority of patients (37.5%) belongs to 41-50 years of age. And among PTB suspects of HIV negative patients the age distribution were higher with majority of about 50% were above the age of 50 years.

Chi square test was applied to these two groups to compare and analyses the difference.

TABLE 3: AGE DISTRIBUTION AMONG PTB SUSPECTS,BASED ON HIV STATUS

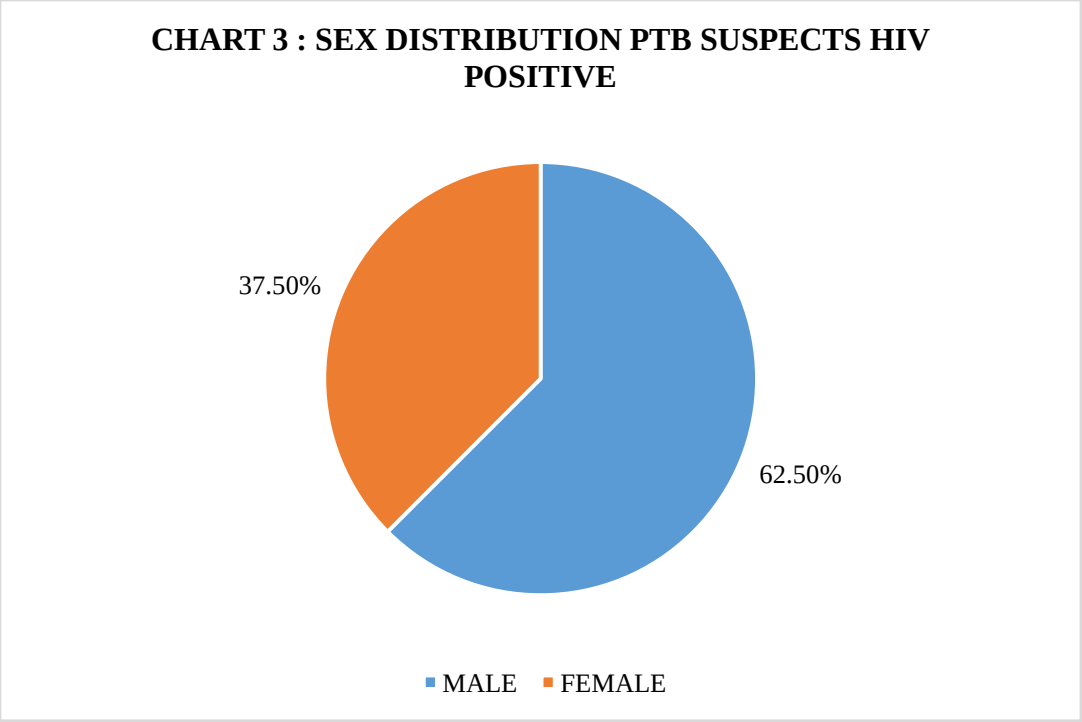
AGE	Pulmonary TB suspecting (HIV +ve)		Pulmonary TB suspecting(HIV-ve)		Total		Statistical inference
	n	%	n	%	n	%	
Below 20yrs	1	2.5%	11	27.5%	12	15.0%	X^2=16.517 Df=5 .006<0.05 Significant
21 to 30yrs	6	15.0%	4	10.0%	10	12.5%	
31 to 40yrs	10	25.0%	9	22.5%	19	23.8%	
41 to 50yrs	15	37.5%	4	10.0%	19	23.8%	
51 to 60yrs	6	15.0%	7	17.5%	13	16.3%	
61yrs & above	2	5.0%	5	12.5%	7	8.8%	
Total	**40**	**100.0%**	**40**	**100.0%**	**80**	**100.0%**	

CONCLUSION

The majority of patients suspecting of pulmonary tuberculosis in HIV positive based on chest X ray and clinical findings were in a lower age group

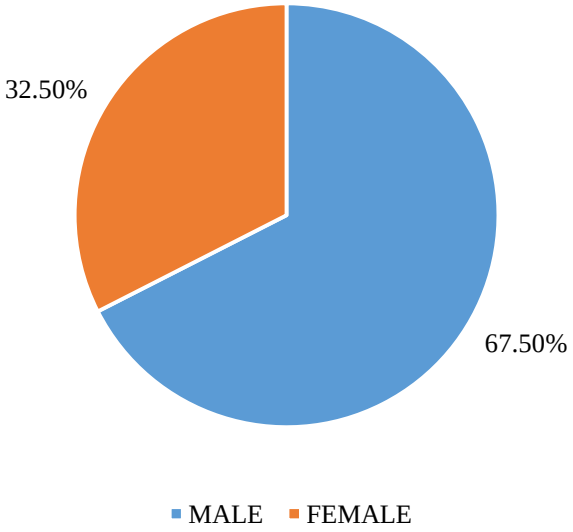
when compared to HIV negative patients when analyzed with Chi square testing using SPSS software.

5.1B: SEX DISTRIBUTION



Among PTB suspecting patients with HIV positivity, 15 out of 40(37.5%) were females, 25 out of 40 patients(62.5%) were males.

CHART 4:SEX DISTRIBUTION PULMONARY TB SUSPECTS HIV NEGATIVE



Among PTB suspects with HIV negativity,13 out of 40 patients(32.5%) were females, 27 out of 40 (67.5%) were males.

That is, there was an increased number of male patients in PTB suspects for HIV negative patients when compared to HIV positive patients. This was analysed using Chi square test and found statistically insignificant.

TABLE 4: SEX DISTRIBUTION AMONG PTB SUSPECTS, BASED ON HIV STATUS

SEX	Pulmonary TB suspecting (HIV +ve)		Pulmonary TB suspecting (HIV-ve)		Total		Statistical inference
	n	%	n	%	n	%	
Male	25	62.5%	27	67.5%	52	65.0%	X^2=.220 Df=1 .639>0.05 Not Significant
Female	15	37.5%	13	32.5%	28	35.0%	
Total	**40**	**100.0%**	**40**	**100.0%**	**80**	**100.0%**	

CONCLUSION

There is no statistically significant co relation between suspected PTB patients who are HIV positive and HIV negative based on sex distribution, when analysed using Chi square test SPSS software.

5.1C: BMI DISTRIBUTION

Mean BMI of the study group was 19. So BMI was categorized as two groups, BMI <19 and >19.Among HIV positive, BMI <19 were predominant, 28 out of 40 patients(70%),and HIV negative group, BMI >19 were predominant, 27 out of 40 patients(67.5%)

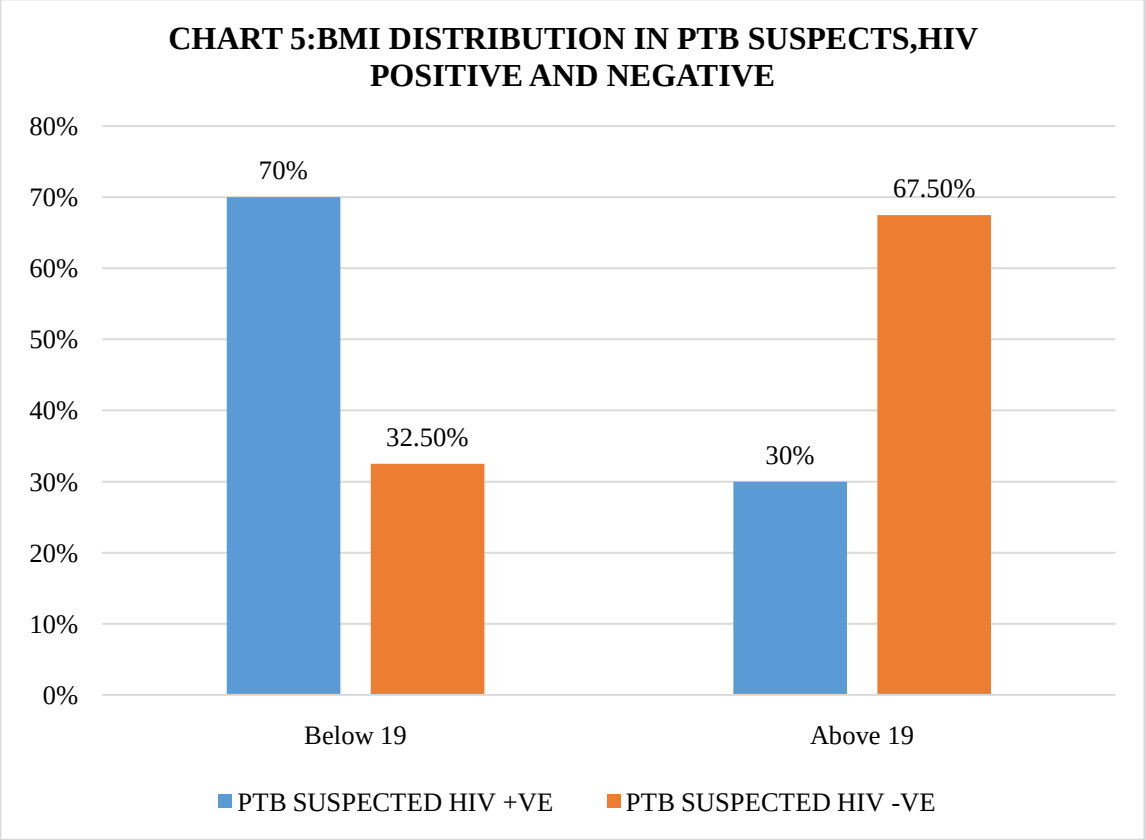


TABLE 5: BMI DISTRIBUTION AMONG PTB SUSPECTING PATIENTS, BASED ON HIV STATUS

BMI	PTB SUSPECTING (HIV +ve)		PTB SUSPECTING (HIV-ve)		Total		Statistical inference
	n	%	n	%	n	%	
Below 19	28	70.0%	13	32.5%	41	51.3%	X^2=11.257 Df=1 .001<0.05 Significant
Above 19	12	30.0%	27	67.5%	39	48.8%	
Total	**40**	**100.0%**	**40**	**100.0%**	**80**	**100.0%**	

CONCLUSION

Mean BMI was 18.39 with a standard deviation of 2.35 among PTB suspecting HIV positive patients and it was 20.95 and 1.54 respectively in HIV negative patients.

There was statistically significant co relation with the finding that the patients suspecting PTB among HIV negative individuals have a higher BMI than HIV positive, when analyzed using Chi square testing, SPSS software.

5.1D: DETECTION WITH FLUORESCENT LED MICROSCOPY

When LED fluorescent microscopy test was used to detect the pulmonary TB suspected, ZN smear negative patients in 40 HIV positive patients, the results were obtained as32 out of 40 patients(80%) were AFB negative, 6 out of 40(15%) were AFB 1+ and 2 patients of 40(5%) were AFB 2+.

When the same method was applied in HIV negative patients with suspected PTB, the results were,31 patients out of 40 (77.5%) was of AFB negative, 3 patients(7.5%) were of AFB 1+,3 patients out of 40(7.5%) were AFB 2+ and the last 7.5% were AFB3+.

CHART 6: DETECTION WITH LED MICROSCOPY IN PTB SUSPECTING HIV(+)

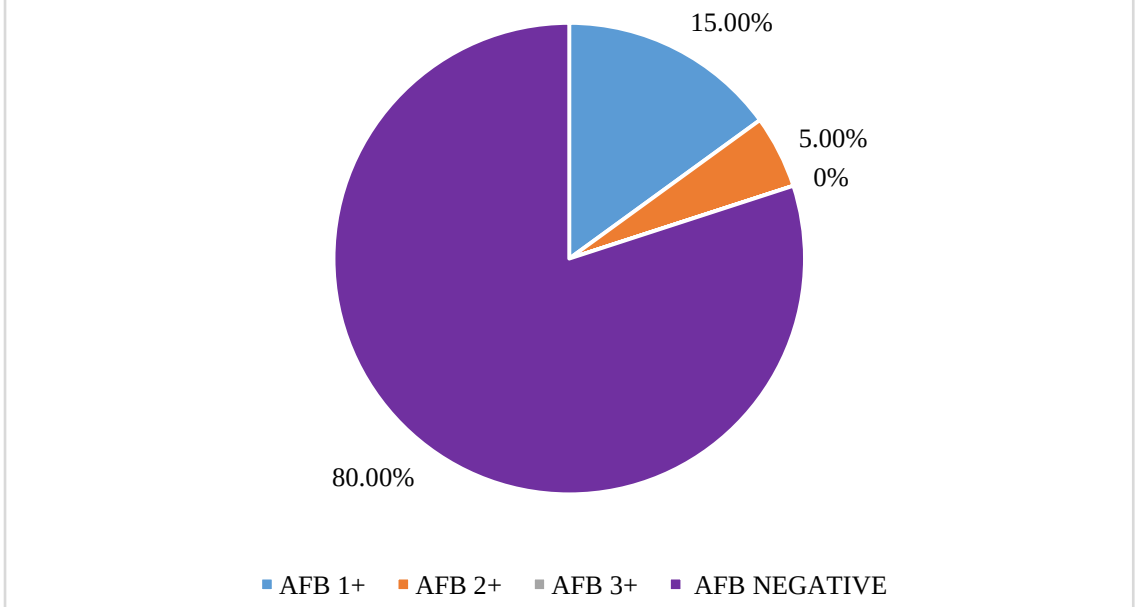


CHART 7: DETECTION WITH LED MICROSCOPY IN PTB SUSPECTING HIV (-)

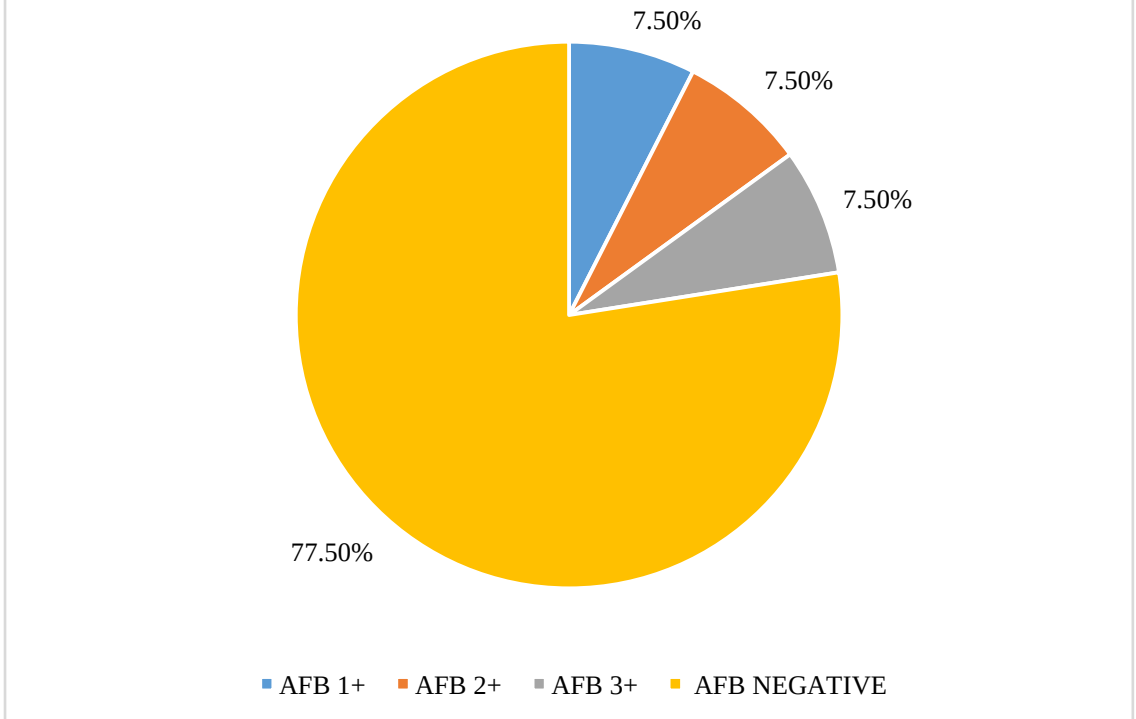


TABLE 6: DETECTION OF PTB WITH FLOURESCENT LED MICROSCOPY, BASED ON HIV STATUS

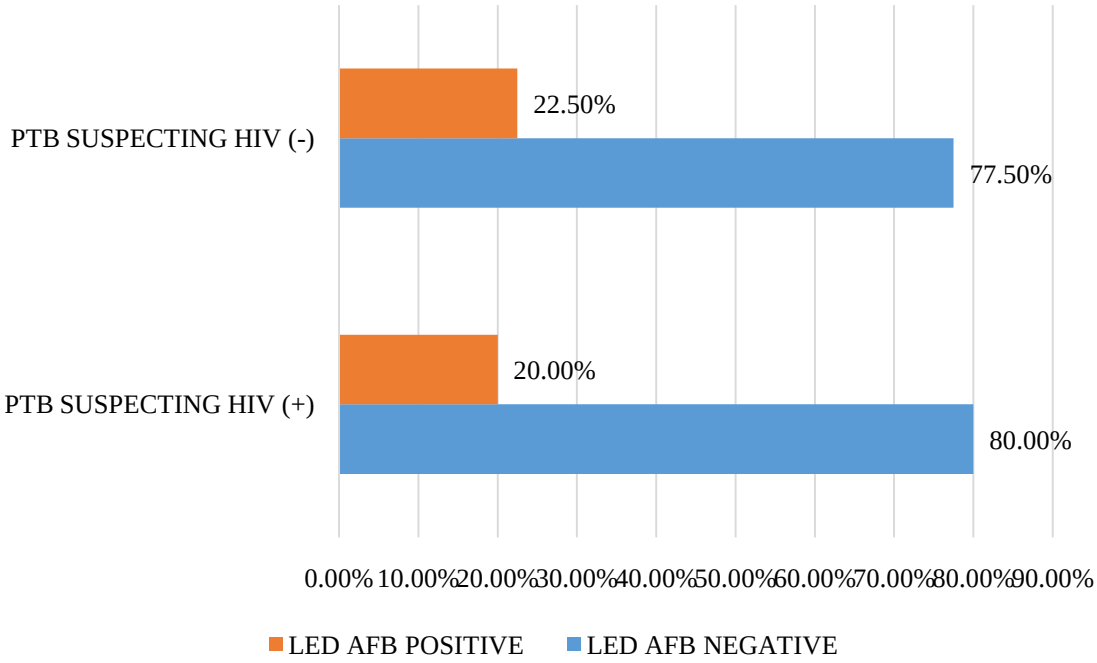
FLOURESCENT LED MICROSCOPY RESULTS	HIV POSITIVE		HIV NEGATIVE		Total		Statistical inference
	n	%	n	%	n	%	
AFB 1+	6	15.0%	3	7.5%	9	11.3%	X^2=4.216
AFB 2+	2	5.0%	3	7.5%	5	6.3%	Df=3
AFB 3+	0	0%	3	7.5%	3	3.8%	.239>0.05
NEG	32	80.0%	31	77.5%	63	78.8%	Not
Total	**40**	**100.0%**	**40**	**100.0%**	**80**	**100.0%**	Significant

CONCLUSION

The increased detection of PTB with LED fluorescent microscopy in HIV negative patients when compared to HIV positive patients were statistically insignificant when Chi square test was applied using SPSS software.

The results with fluorescent LED microscopy were categorized as AFB positive and AFB negative.AFB positive includes all patients detected as AFB 1+,AFB 2+ and AFB 3+ and the rest as negative.

CHART 8: DETECTION OF PTB SUSPECTS BY LED MICROSCOPY,HIV(+)&(-)



The detection of PTB in ZN smear negative PTB suspects by LED fluorescent microscopy was,9 out of 40(22.5%) patients among HIV positive patients and 8 out of 40(20%) among HIV negative patients. So there is a seemingly better detection with LED fluorescent microscopy among HIV negative patients.

TABLE 7: DETECTION OF PTB WITH FLOURESCENT LED MICROSCOPY, BASED ON HIV STATUS

LED FLOURESCENT MICROSCOPY AFB	**PULMONARY TB SUSPECTING HIV(+)**		**PULMONARY TB SUSPECTING HIV(-)**		**Total**		**Statistical inference**
	n	**%**	**n**	**%**	**n**	**%**	
Negative	32	80.0%	31	77.5%	63	78.8%	X^2=0.075 Df=1 .785>0.05 Not Significant
Positive	8	20.0%	9	22.5%	17	21.3%	
Total	**40**	**100.0%**	**40**	**100.0%**	**80**	**100.0%**	

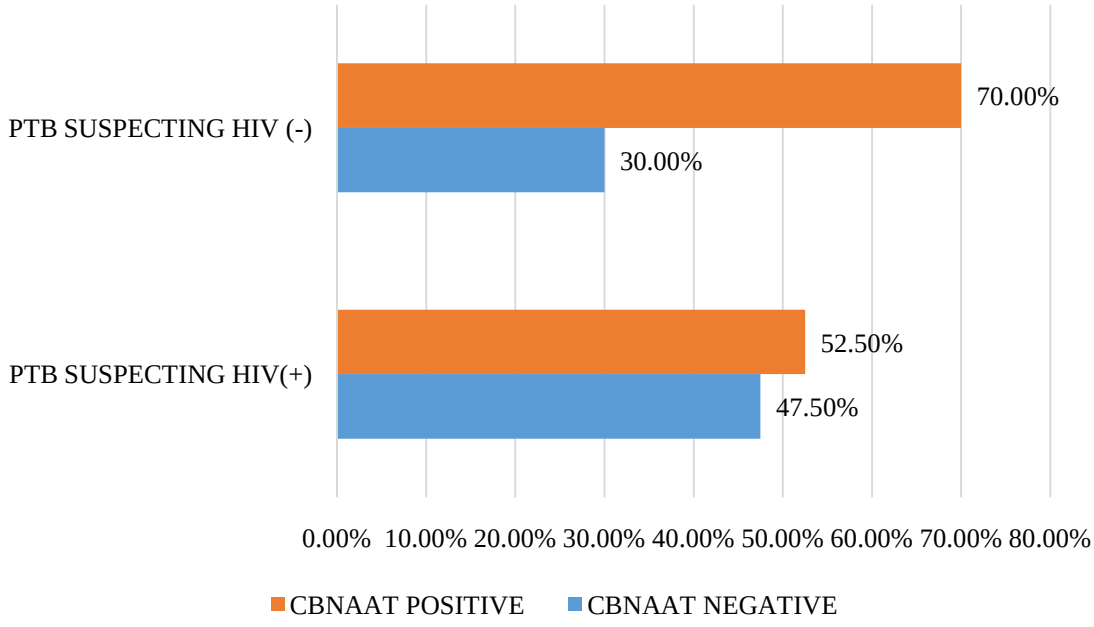
CONCLUSION

The increased detection of PTB with LED fluorescent microscopy in HIV negative patients when compared to HIV positive patients were statistically insignificant when Chi square test was applied using SPSS software

5.1E: DETECTION WITH CBNAAT

When CBNAAT was used to detect the PTB in sputum samples of ZN smear negative patients with HIV(n=40) and without HIV(n=40),CBNAAT was positive in 21 HIV positive and 28 HIV negative patients. That is, among HIV positive patients the detection of PTB was 48% using CBNAAT.(52% were negative).In HIV negative patients CBNAAT detected 70% patients as positive and 30% as negative. The seemingly increased detection with CBNAAT in HIV negative patients were analyzed against HIV positive.

CHART 9: COMPARISON OF DETECTION BY CBNAAT,PTB SUSPECTS,HIV(+)&HIV(-)



In HIV negative patients, CBNAAT detected in 28 out of 40 patients(70%) of pulmonary TB and in HIV positive patients, the detection was 21 out of 40 patients.(52.5%.) So there is a seemingly better detection of PTB with CBNAAT among HIV negative patients, and was analyzed statistically.

TABLE 8: DETECTION OF PTB WITH CBNAAT, BASED ON HIV STATUS

CBNAAT	PTB SUSPECTING HIV (+VE)		PTB SUSPECTING HIV(-)		Total		Statistical inference
	n	%	n	%	n	%	
Negative	19	47.5%	12	30.0%	31	38.8%	X^2=2.581 Df=1 .108>0.05 Not Significant
Positive	21	52.5%	28	70.0%	49	61.3%	
Total	**40**	**100.0%**	**40**	**100.0%**	**80**	**100.0%**	

CONCLUSION

The increased detection of PTB with CBNAAT in HIV negative patients when compared to HIV positive patients was statistically insignificant when Chi square test was applied using SPSS software.

This is in accordance with the study done by Boheme et al.(5)

5.1F: DETECTION OF RIFAMPICIN RESISTANCE WITH CBNAAT:

Out of the CBNAAT positive patients of both the groups, Rifampicin resistance was detected for three patients. One was an HIV positive patient and other 2 were HIV negative.

TABLE 9: DETECTION OF RIFAMPICIN RESISTANCE OF PTB WITH CBNAAT, BASED ON HIV STATUS

RIFAMPICIN RESISTANCE	HIV POSITIVE		HIV NEGATIVE		Total		Statistical inference
	n	%	n	%	n	%	
NA	19	47.5%	12	30.0%	31	38.8%	X^2=2.697 Df=2 .260>0.05 Not Significant
Detected	1	2.5%	2	5.0%	3	3.8%	
Not detected	20	50.0%	26	65.0%	46	57.5%	
Total	**40**	**100.0%**	**40**	**100.0%**	**80**	**100.0%**	

CONCLUSION

There was no statistically significant co relation in the detection of Rifampicin resistance by CBNAAT in PTB, HIV positive and negative groups when analyzed with Chi square testis's software.

5.1G: DETECTION OF ZN SMEAR NEGATIVE PTB IN HIV PATIENTS AND NON HIV PATIENTS GROUP, COMPARISON BETWEEN CB NAAT AND FLOURESCENT LED MICROSCOPY:

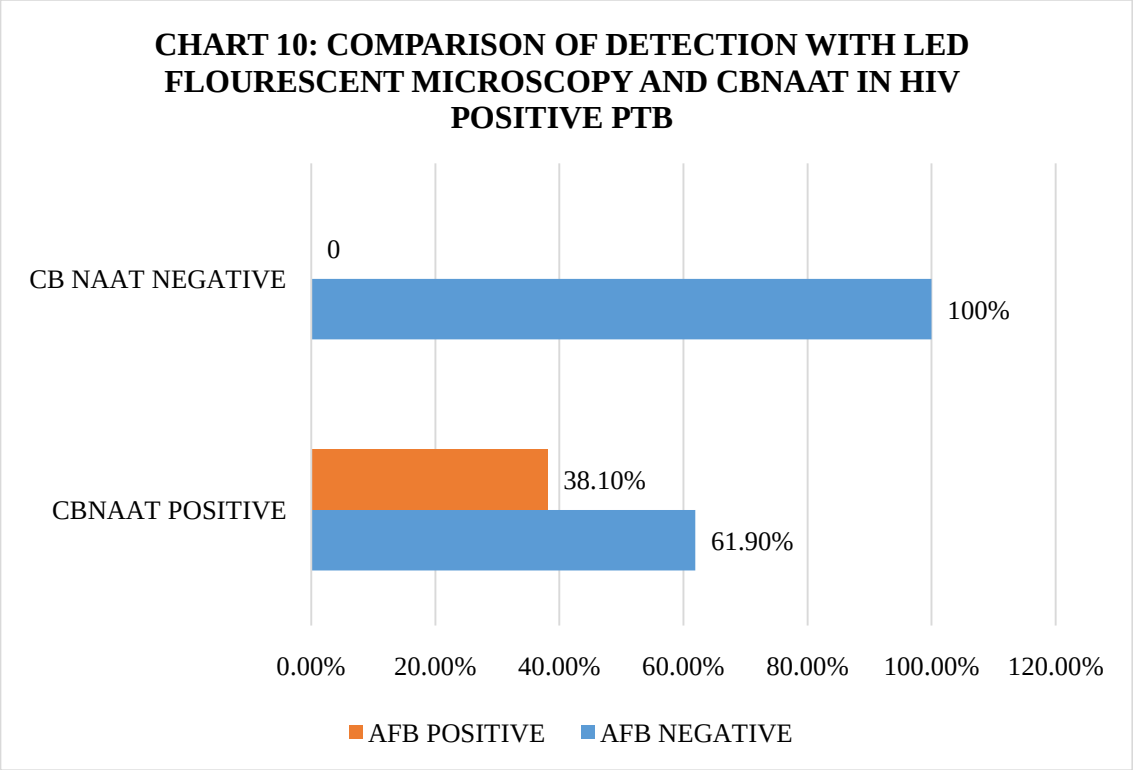
Based on the LED microscopy results and CBNAAT results, all the patients were grouped as

1. FLOURESCENT LED MICROSCOPY POSITIVE,CBNAAT POSITIVE (M +ve & CB+ve)
2. FLOURESCENT LED MICROSCOPY NEGATIVE,CBNAAT POSITIVE(M-ve & CB+ve)
3. FLOURESCENT LED MICROSCOPY AND CB NAAT NEGATIVE(M –ve & CB -ve)

In HIV positive patients, LED fluorescent microscopy positive and CB NAAT positivity were 8 were, LED fluorescent microscopy positive and CB NAAT negative patients were 13 and LED fluorescent microscopy negative and CB NAAT negativity were 19.

In HIV negative, these were 9,18 and13 patients respectively. So a difference were noted in these two groups with higher fluorescent LED microscopy smear negative PTB detection with CBNAAT in HIV negative patients compared to HIV positive.

HIV POSITIVE



LED fluorescent microscopy was positive in 8 out of 21 patients(38.1%),and all of them were CB NAAT positive. CB NAAT detected 13 out of 21 (61.9%) of ZN negative PTB patients. All CB NAAT negative patients were also fluorescent AFB negative.

PTB SUSPECTING HIV POSITIVE PATIENTS = 40

FLOURESCENT MICROSCOPY AFB * CBNAAT

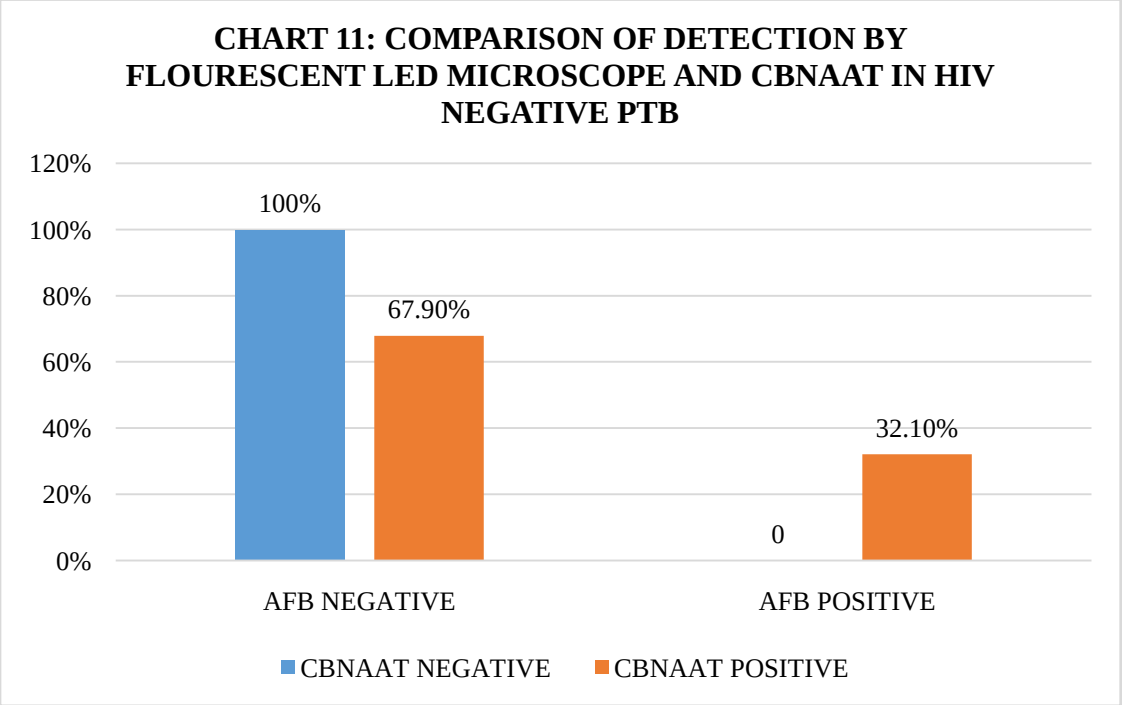
TABLE 10: COMPARISON OF PTB DETECTION BY LED FLUORESCENT MICROSCOPY AND CBNAAT AMONG HIV POSITIVE PATIENTS

LED MICROSCOPY AFB	CBNAAT DETECTION						Statistical inference
	Negative		Positive		Total		
	n	%	n	%	n	%	
Negative	19	100%	13	61.9%	32	80.0%	X^2=9.048 df=1 .003<0.05 Significant
Positive	0	0	8	38.1%	8	20%	
Total	**19**	**100%**	**21**	**100%**	**40**	**100%**	

CONCLUSION

There was a better detection of PTB with CBNAAT when compared to Fluorescent LED microscopy in ZN smear negative PTB in HIV positive patients. This was statistically significant when analyzed with Chi square testing using SPSS software.

HIV NEGATIVE



All of the patients detected by light microscopy were CBNAAT positive. But out of the total patients detected by CBNAAT, only 32.1% were AFB positive. So there seems to be a better detection with CBNAAT when compared to AFB detection by LED fluorescent microscopy.

5.1H DETECTION OF ZN SMEAR NEGATIVE PTB IN HIV PATIENTS AND NON HIV PATIENTS, COMPARISON BETWEEN CB NAAT AND FLOURESCENT LED MICROSCOPY

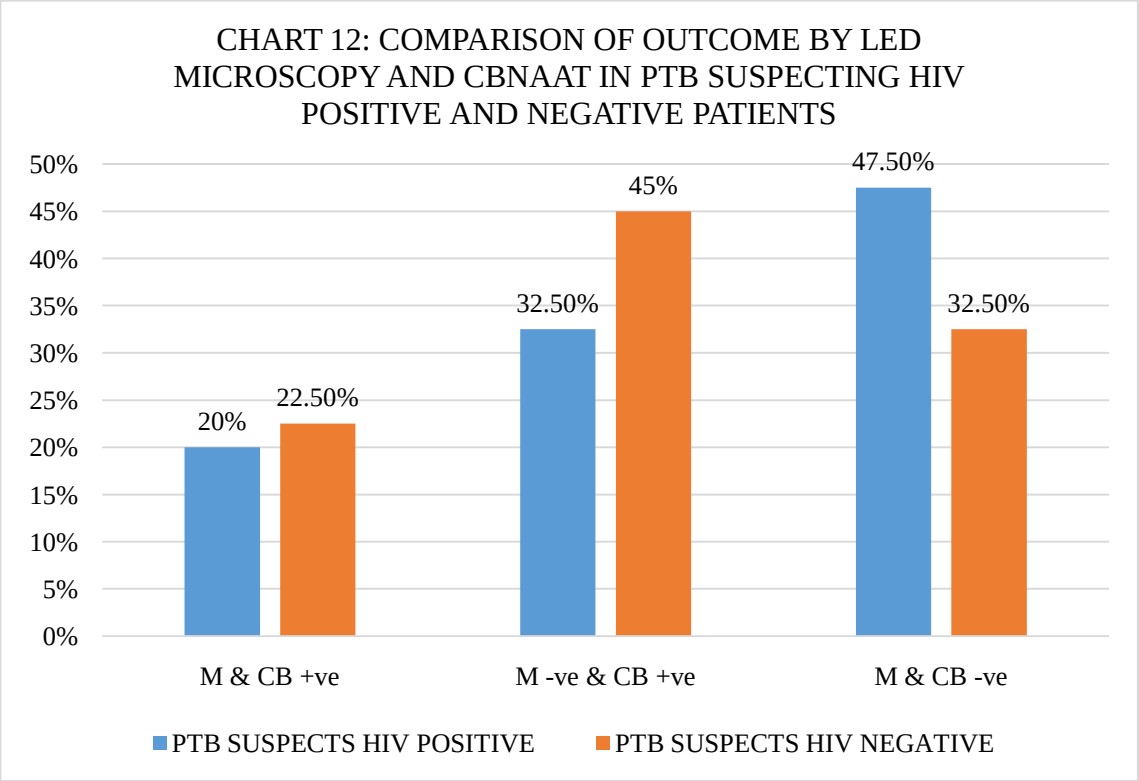


TABLE 11: COMPARISON OF OUTCOME OF DETECTION WITH FLUORESCENT LED MICROSCOPY AND CBNAAT WITH HIV STATUS OF PATIENTS

Outcome	PULMONARY TB SUSPECTING PATIENTS						Statistical inference
	(HIV +ve)		(HIV-ve)		Total		
	N	%	n	%	n	%	
M+ve& CB +ve	8	20%	9	22.5%	17	21.3%	X^2=1.990 df=2 .370>0.05 Not Significant
M -ve& CB +ve	13	32.5%	18	45%	31	38.8%	
M-ve& CB -ve	19	47.5%	13	32.5%	32	40%	
Total	**40**	**100%**	**40**	**100%**	**80**	**100%**	

CONCLUSION

There was no statistically significant co relation in HIV positive and HIV negative patients with the outcome of fluorescent LED microscopy and CBNAAT detection in suspected PTB, when analyzed with Chi square testing using SPSS software.

This was in accordance with the studies conducted by Boheme et al.(5)

5.2 EXTRA PULMONARY TUBERCULOSIS

A total of 50 Extra Pulmonary Tuberculosis patients were included in the study. Out of this,30 were FNAC specimens from suspected tuberculosis lymphadenitis, of which 15 were HIV positive, and 15 HIV negative.

The rest 20 specimens were pleural fluid aspirates. Out of which 10 were from HIV positive individuals and 10 from HIV negative.

They were also subjected to LED microscopy analysis, and CBNAAT.

5.2.1DETECTION WITH FLUORESCENT LED MICROSCOPY OF FNAC SPECIMEN OF TB LYMPHADENITIS

The detection with Fluorescent LED microscopy in 15 HIV positive individuals in FNAC specimen were,

AFB 1+ were 2

AFB 2+ were 2

AFB 3+ was 1 and AFB negative were 10 out of 15 patients.

In HIV negative, AFB 1+ were 5 patients, AFB 2+ was 1 patient out of 15(6.70%),AFB 3+ were 1 out of 15(6.7%) and AFB negative were 8 patients(53.3%)

CHART 13:DETECTION OF TUBERCULOUS LYMPHADENITIS WITH LED FLOURESCENT MICROSCOPY IN HIV POSITIVE

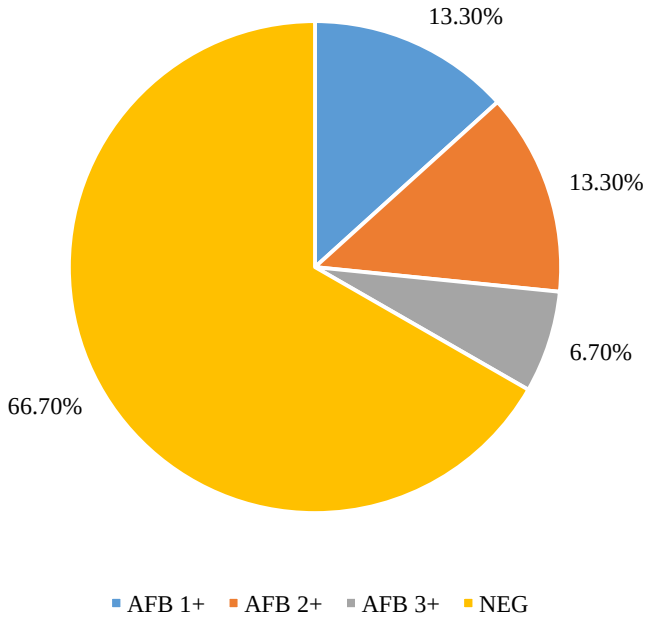
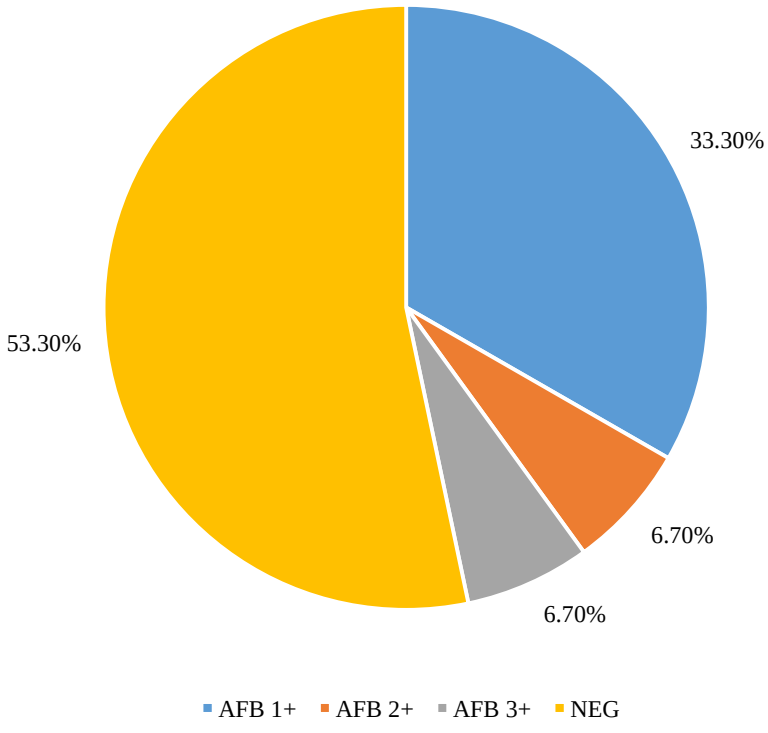
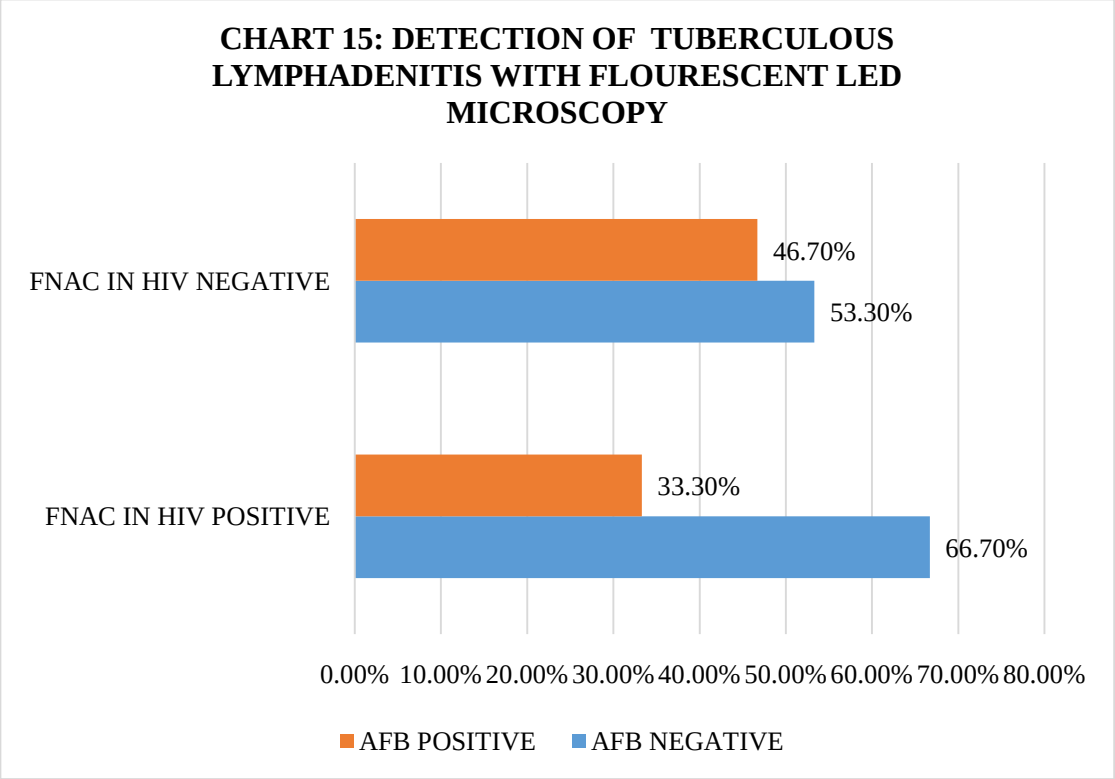


CHART 14:DETECTION OF TUBERCULOUS LYMPHADENITIS WITH LED FLOURESCENT MICROSCOPY IN HIV NEGATIVE



DETECTION OF TUBERCULOUS LYMPHADENITIS WITH FLOURESCENT LED MICROSCOPY, BASED ON HIV STATUS



Tuberculous lymphadenitis detection among HIV negative patients was 46%, and among HIV positive patients, it was 33%.

TABLE 12: DETECTION OF TUBERCULOUS LYMPHADENITIS WITH FLOURESCENT LED MICROSCOPY, BASED ON HIV STATUS

MICROSCOPY AFB	FNAC (HIV+)		FNAC (HIV-)		Total		Statistical inference
	n	%	n	%	n	%	
1+	2	13.3%	5	33.3%	7	23.3%	X^2=1.841 Df=3 .606>0.05 Not Significant
2+	2	13.3%	1	6.7%	3	10.0%	
3+	1	6.7%	1	6.7%	2	6.7%	
NEG	10	66.7%	8	53.3%	18	60.0%	
Total	**15**	**100.0%**	**15**	**100.0%**	**30**	**100.0%**	

CONCLUSION

There was no statistically significant co relation in HIV positive and HIV negative patients with the detection of Tuberculous lymphadenitis with LED fluorescent microscopy, when analyzed with Chi square testing using SPSS software.

5.2.2 DETECTION WITH CBNAAT OF FNAC SPECIMEN, TB LYMPHADENITIS

TABLE 13: DETECTION OF TUBERCULOUSLYMPHADENITIS WITH FLOURESCENT LED MICROSCOPY, BASED ON HIV STATUS

CBNAAT POSITIVE TYPE	FNAC (HIV+)		FNAC (HIV-)		Total		Statistical inference
	n	%	n	%	n	%	
Negative	4	26.7%	6	40.0%	10	33.3%	X^2=0.600 Df=1 .439>0.05 Not Significant
Positive	11	73.3%	9	60.0%	20	66.7%	
Total	**15**	**100.0%**	**15**	**100.0%**	**30**	**100.0%**	

CHART 16:CBNAAT DETECTION TUBERCULOUS LYMPHADENITIS, HIV POSITIVE

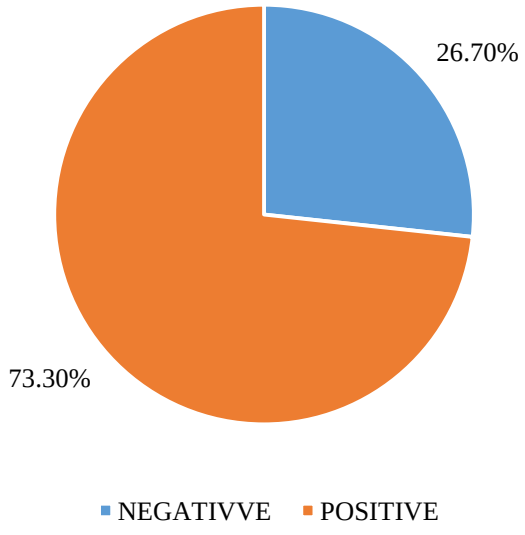


CHART 17:CBNAAT DETECTION TUBERCULOUS LYMPHADENITIS, HIV POSITIVE

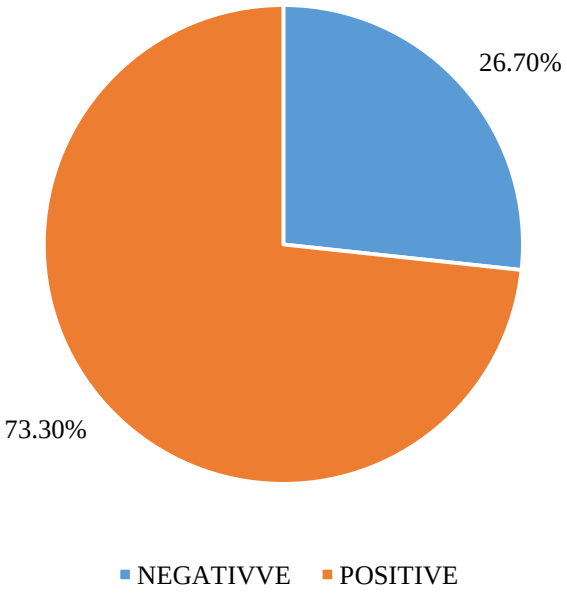
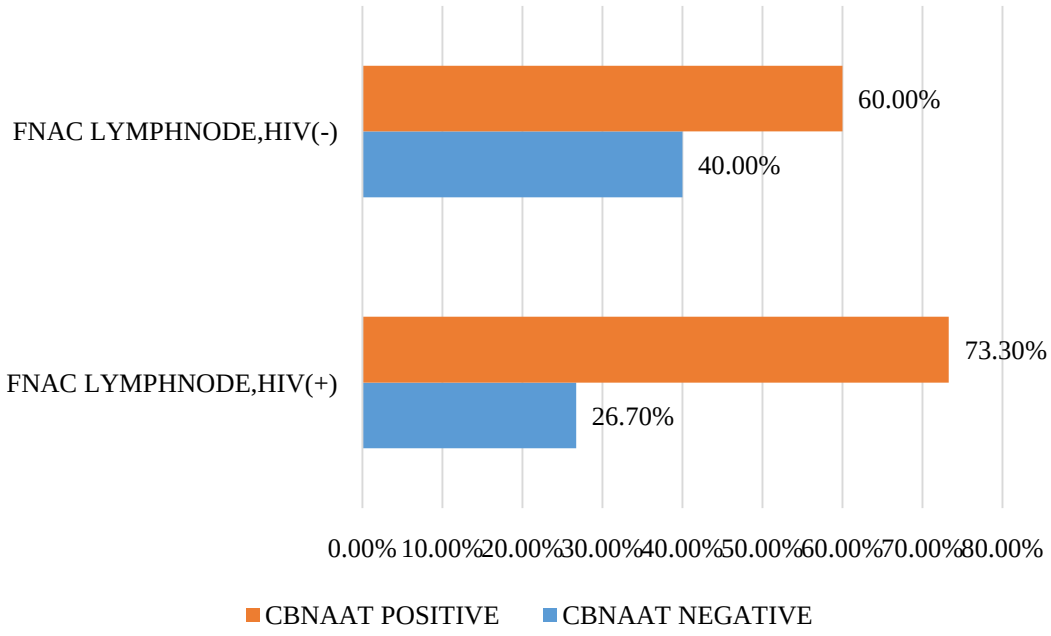


CHART 18:DETECTION OF TUBERCULOUS LYMPHADENITIS WITH CBNAAT IN HIV POSITIVE AND NEGATIVE PATIENTS



CB NAAT showed a positive result of 11 out of 15 patients (73.3%) in HIV positive patients and 9 out of 15 patients (60%) in HIV negative patients in detection of tuberculosis lymphadenitis.

CONCLUSION

There was no statistically significant difference in HIV positive and HIV negative patients with the detection of tuberculous lymphadenitis with LED fluorescent microscopy, when analysed with Chi square testing using SPSS software.

5.2.3 COMPARISON BETWEEN CBNAAT AND LED MICROSCOPY RESULTS IN TUBERCULOUS LYMPHADENITIS

Out of 15 patients of HIV positive suspecting tuberculosis lymphadenitis, Fluorescent LED microscopy was compared to CBNAAT results.

TABLE 14: COMPARISON OF TUBERCULOUS LYMPHADENITIS DETECTION BY LED FLUORESCENT MICROSCOPY AND CBNAAT AMONG HIV POSITIVE PATIENTS

FLOURESCENT LED MICROSCOPY	**CBNAAT RESULT**						**Statistical inference**
	Negative		**Positive**		**Total**		
	n	**%**	**N**	**%**	**n**	**%**	
Negative	4	100%	6	54.5%	10	66.7%	X^2=2.727 df=1 .099>0.05 Not Significant
Positive	0	0	5	45.5%	5	33.3%	
Total	**4**	**100%**	**11**	**100%**	**15**	**100%**	

Out of 15 specimens,

LED fluorescent microscopy negative and CB NAAT negative were 4

LED fluorescent microscopy negative and CB NAAT positive were 5

LED fluorescent microscopy negative CBNAAT positive were 6

Statistical analysis between the results were done using Chi square test.

CONCLUSION

There was no statistically significant difference between the detection of tuberculosis lymphadenitis using CB NAAT and fluorescent LED microscopy among HIV positive patients. This was against the tests quoted. Probably because of low sample size.

CHART 19: COMPARISON OF CBNAAT AND LED AFB RESULTS IN TUBERCULOUS LYMPHADENITIS IN HIV POSITIVE

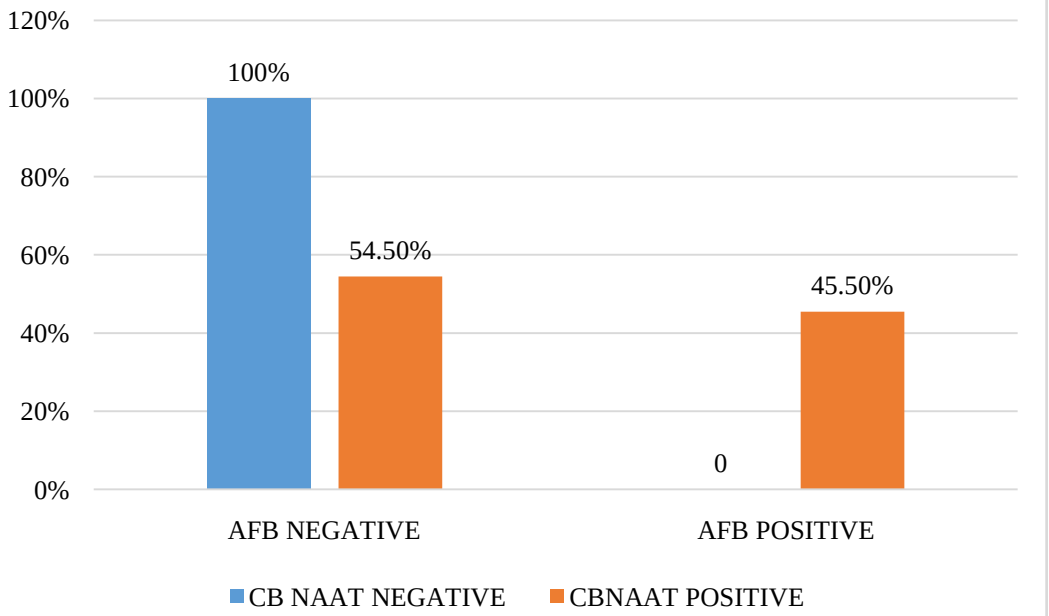


Chart shows that, all the CBNAAT negative patients were AFB negative. Among CB NAAT positivity,8 out of 15(54.5%)were AFB negative and 7 out of 15(45.5%)were AFB positive.

HIV NEGATIVE PATIENTS

In the other group of HIV negative patients, with suspecting tuberculous lymphadenitis,

LED fluorescent microscopy negative and CB NAAT negative were 6

LED fluorescent microscopy negative and CB NAAT positive were 2

LED fluorescent microscopy negative and CBNAAT positive were 7

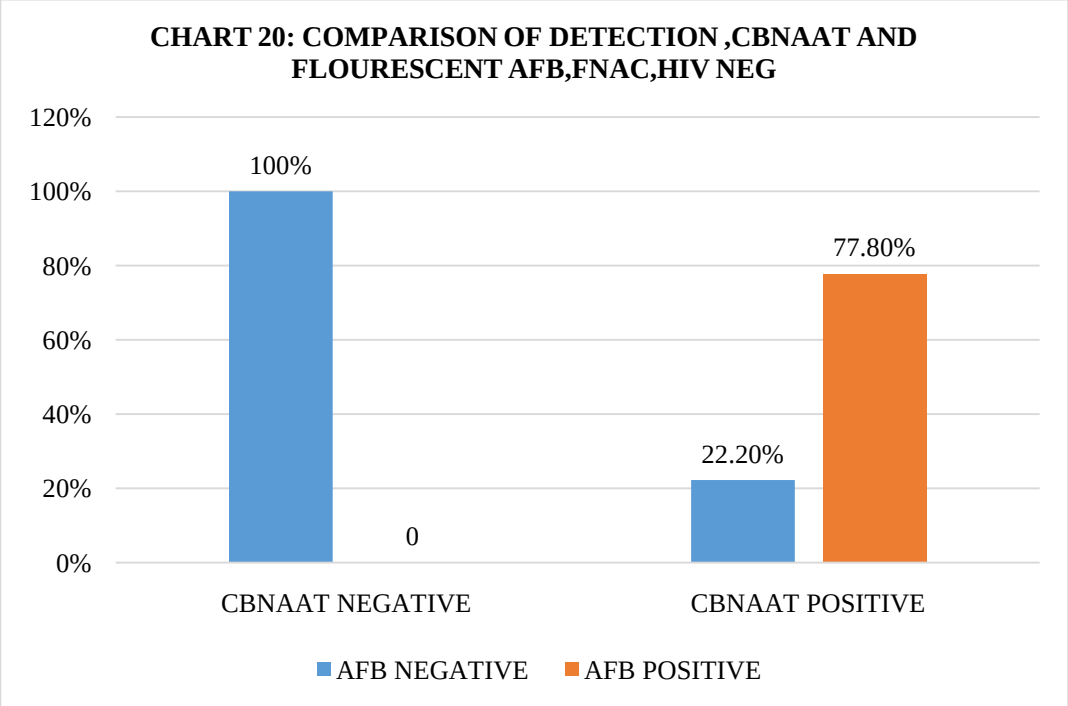


Chart shows that, all the CB NAAT negative patients were AFB negative. Out of the CB NAAT positive patients, 7 out of 9 patients(77.8%) were AFB positive and 2 out of 15 patients 22.2% were AFB negative.

TABLE 15: COMPARISON OF TUBERCULOUS LYMPHADENITIS DETECTION BY LED FLUORESCENT MICROSCOPY AND CBNAAT AMONG HIV NEGATIVE PATIENTS

LED FLOURESCENT MICROSCOPY AFB	**CBNAAT RESULT**						**Statistical inference**
	Negative		**Positive**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	
AFB NEGATIVE	6	100%	2	22.2%	8	53.3%	X^2=8.750
AFB POSITIVE	0	0	7	77.8%	7	46.7%	df=1
Total	**6**	**100%**	**9**	**100%**	**15**	**100%**	.003<0.05 Significant

CONCLUSION

There is statistically significant better detection with CBNAAT compared to LED microscopy, in patients who are HIV negative with tuberculous lymphadenitis.(13),analyzed with Chi square test,SPSS software.

PLEURAL FLUID

20 patients were analysed in this group. 10 were HIV positive and 10 were HIV negative.

5.2.4 FLOURESCENT LED DETECTION OF TB PLEURAL EFFUSION

In HIV positive patients LED microscopy detected 9 out of 10(90%) samples as AFB negative and 1 out of 10(10%) patients as AFB 1+ positive.

In HIV negative patients, this was 8 out of 10(80%) negative and two of 10(20%) patients were AFB 1+ that is, scanty positivity.

CHART 21:TUBERCULOUS PEURAL EFFUSION DETECTION,LED FLUORESCENT MICROSCOPY,HIV (+)

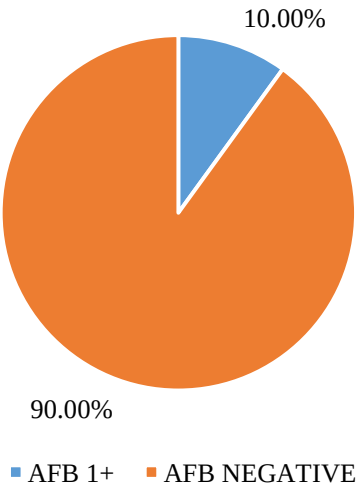


CHART 22:TUBERCULOUS PLEURAL EFFUSION DETECTION,LED FLOURESCENT MICROSCOPY,HIV(-)

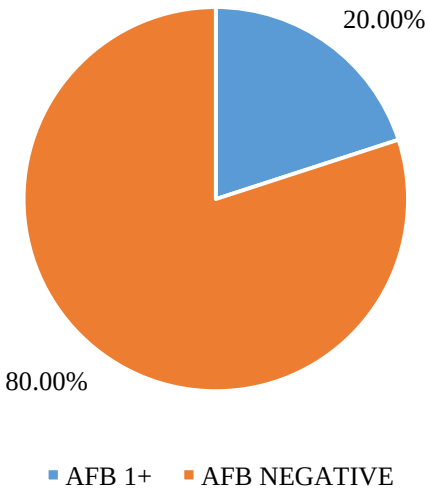


TABLE 16: DETECTION OF TUBERCULOUS PLEURAL EFFUSION WITH FLOURESCENT LED MICROSCOPY, BASED ON HIV STATUS

FLOURESCENT LED MICROSCOPY AFB	PF (HIV+)		PF (HIV-)		Total		Statistical inference
	n	%	n	%	n	%	
1+	1	10.0%	2	20.0%	3	15.0%	X^2=0.392 Df=1 .531>0.05 Not Significant
NEG	9	90.0%	8	80.0%	17	85.0%	
Total	**10**	**100.0%**	**10**	**100.0%**	**20**	**100.0%**	

CONCLUSION

There is no statistically significant difference in detection of tuberculous pleural effusion with LED microscopy between HIV positive and negative patients, using Chi square test, SPSS software.

5.2.5 CB NAAT DETECTION OF TB PLEURAL EFFUSION

Of the 10 pleural fluid samples from HIV positive patients, 8 out of 10 (80%) were CBNAAT negative and 2 out of 10 patients,(20%) were CBNAAT positive.

In HIV negative patients, CBNAAT was positive in 3 out of 10 patients(30%) samples and 7 out of 10(70%) were CBNAAT negative.

CHART 23: DETECTION OF TB PLEURAL EFFUSION,CBNAAT,HIV POSITIVE

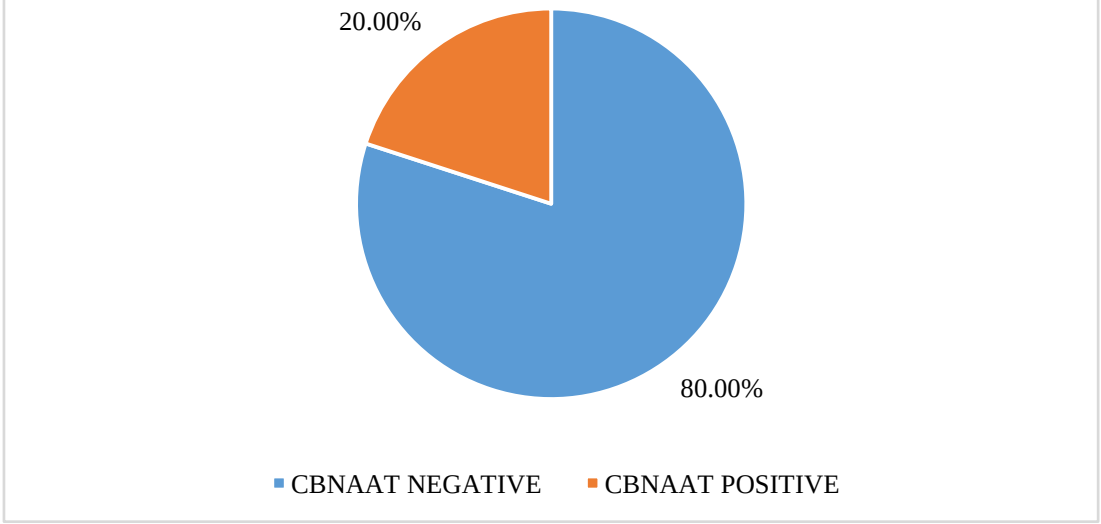


CHART 24:DETECTION OF TB PLEURAL EFFUSION,CBNAAT,HIV NEGATIVE

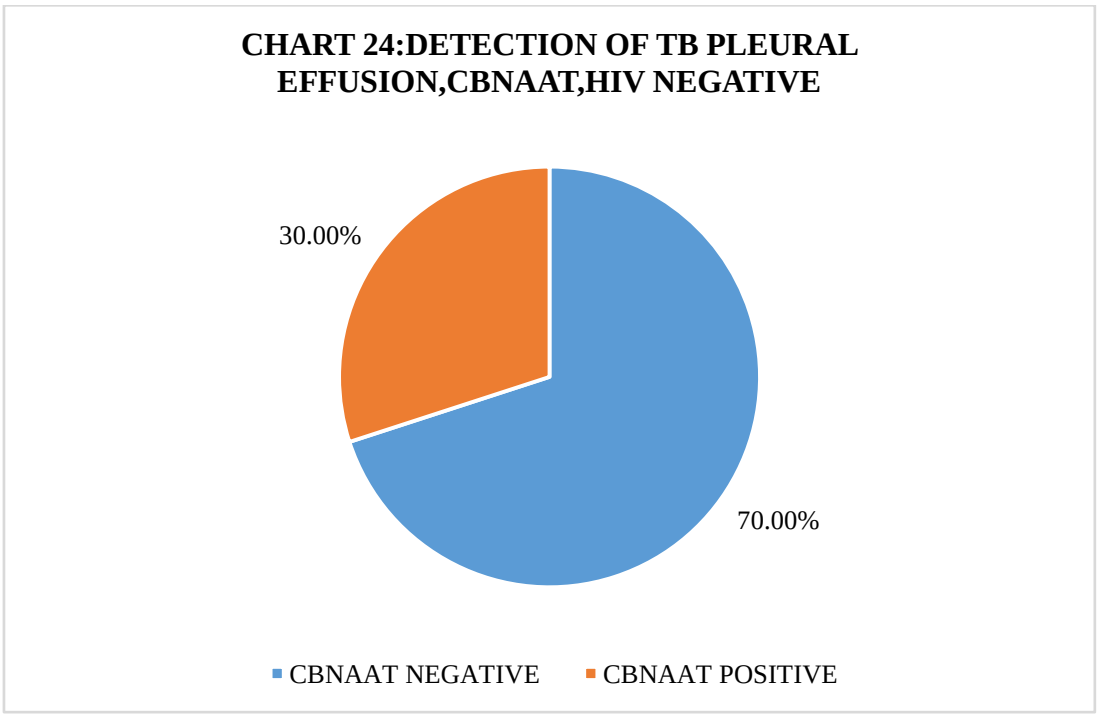


TABLE 17: DETECTION OF TUBERCULOUS PLEURAL EFFUSION WITH CB NAAT, BASED ON HIV STATUS

CBNAAT RESULT	**PLEURAL FLUID (HIV+)**		**PLEURAL FLUID (HIV-)**		**Total**		**Statistical inference**
	n	**%**	**n**	**%**	**n**	**%**	
Negative	8	80.0%	7	70.0%	15	75.0%	X^2=0.267 Df=1 .606>0.05 Not Significant
Positive	2	20.0%	3	30.0%	5	25.0%	
Total	**10**	**100.0%**	**10**	**100.0%**	**20**	**100.0%**	

CONCLUSION

There is no statistically significant better detection of TB pleural effusion in HIV negative individuals, when compared to HIV positive, when analyzed with Chi square test, using SPSS software.

5.2.6 COMPARISON OF DETECTION BETWEEN LED FLOURESCENT MICROSCOPY AND CB NAAT

HIV POSITIVE:

Out of 15 specimens,

- LED fluorescent microscopy negative and CB NAAT negative were 8
- LED fluorescent microscopy positive and CB NAAT positive were 1

- LED fluorescent microscopy negative and CB NAAT positive were 1

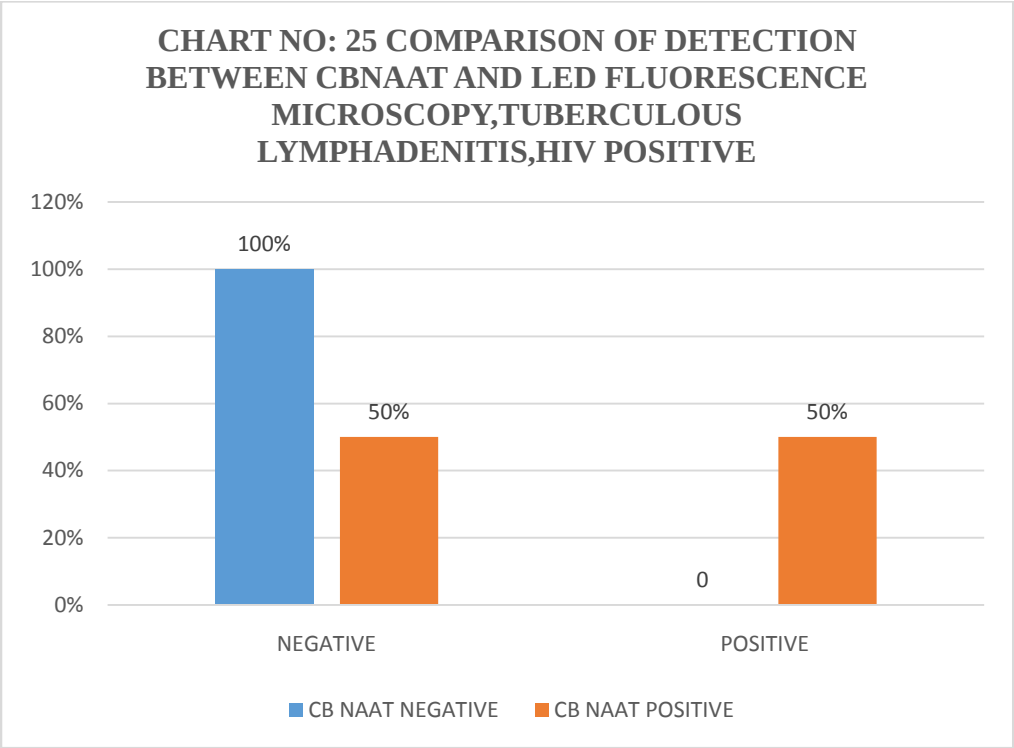


Chart shows that all the AFB positive patients were CB NAAT positive. Out of all the CB NAAT positive patients,7 out of 9, (77.8%) were AFB positive,2 out of 9(22.2%)were AFB negative

TABLE 18: COMPARISON OF TUBERCULOUS PLEURAL EFFUSION DETECTION BY LED FLUORESCENT MICROSCOPY AND CBNAAT AMONG HIV POSITIVE PATIENTS

LED FLOURESCENT MICROSCOPY AFB	CBNAAT POSITIVE TYPE						Statistical inference
	Negative		Positive		Total		
	n	%	n	%	n	%	
Negative	8	100%	1	50%	9	90%	X^2=4.444 df=1 .035<0.05 Significant
Positive	0	0	1	50%	1	50%	
Total	**8**	**100%**	**2**	**100%**	**10**	**100%**	

CONCLUSION

There is s statistically significant better detection with CB NAAT when compared to fluorescent LED microscopy in tuberculous pleural effusion in HIV positive patients.

HIV NEGATIVE

Total number of patients:10

- LED fluorescent microscopy negative and CB NAAT negative were 7(70%)
- LED fluorescent microscopy positive and CB NAAT positive were 2(20%)

- LED fluorescent microscopy negative and CB NAAT positive were 1(10%)

Chart shows that, all CB NAAT negative patients were AFB negative. Out of CB NAAT positivity,1 out of 10(10%) was AFB positive. And 1 out of 10 (10%) was AFB negative.

TABLE 19: COMPARISON OF TUBERCULOUS PLEURAL EFFUSION DETECTION BY LED FLUORESCENT MICROSCOPY AND CBNAAT AMONG HIV NEGATIVE PATIENTS

FLOURESCENT LED MICROSCOPY AFB	**CBNAAT RESULT**						**Statistical inference**
	Negative		**Positive**		**Total**		
	n	**%**	**n**	**%**	**n**	**%**	
Negative	7	100%	1	33.3%	8	80%	X^2=5.833
Positive	0	0	2	66.7%	2	20%	df=1
Total	**7**	**100%**	**3**	**100%**	**10**	**100%**	.016<0.05 Significant

CONCLUSION

There is s statistically significant better detection with CB NAAT when compared to fluorescent LED microscopy in tuberculous pleural effusion in HIV negative patients.

5.2.7 COMPARISON OF OUTCOME OF EXTRA PULMONARY TUBERCULOSIS DETECTION WITH CBNAAT AND LED MICROSCOPY:

TABLE 20: COMPARISON OF OUTCOME OF DETECTION OF EXTRA PULMONARY TUBERCULOSIS WITH FLUORESCENT LED MICROSCOPY AND CBNAAT WITH HIV STATUS OF PATIENTS

Outcome	EXTRA PULMONARY TB						Statistical inference
	HIV +ve		HIV-ve		Total		
	n	%	n	%	n	%	
M +ve& CB +ve	6	24%	9	36%	15	30%	
M -ve& CB +ve	7	28%	3	12%	10	20%	X^2=2.240 df=2 .326>0.05 Not Significant
M-ve& CB -ve	12	48%	13	52%	25	50%	
Total	**25**	**100%**	**25**	**100%**	**50**	**100%**	

CONCLUSION

In Extra Pulmonary Tuberculosis, the results of two tests CBNAAT and LED fluorescence microscopy were not having statistically significant difference in HIV positive and negative patients when analysed with Chi square test, SPSS software.

5.2.8 COMPARISON OF OUTCOME WITH CBNAAT AND LED MICROSCOPY WITH CD4 COUNT:

TABLE 21: COMPARISON OF OUTCOME OF DETECTION WITH FLUORESCENT LED MICROSCOPY AND CBNAAT WITH CD4 COUNT OF PATIENTS WITH HIV.

CD4 COUNT	Outcome of LED flourescent microscopy & CB NAAT								Statistical inference
	M+ve& CB +ve		M -ve& CB +ve		M-ve& CB -ve		Total		
	n	%	n	%	n	%	n	%	
Below 100	4	28.6%	5	25%	5	16.1%	14	21.5%	X^2=5.137 df=6 .526>0.05 Not Significant
101 to 350	6	42.9%	13	65.0%	21	67.7%	40	61.5%	
351 to 500	1	7.1%	1	5.0%	3	9.7%	5	7.7%	
500 & above	3	21.4%	1	5.0%	2	6.5%	6	9.2%	
Total	**14**	**100%**	**20**	**100%**	**31**	**100%**	**65**	**100%**	

One-way ANOVA

CD4 COUNT	Mean	S.D	SS	DF	MS	Statistical inference
Between Groups			224813.746	2	112406.873	F=2.109 .130>0.05 Not Significant
M +ve& CB +ve (n=14)	355.64	358.009				
M -ve& CB +ve (n=20)	215.50	239.130				
M-ve& CB –ve (n=31)	210.84	135.562				
Within Groups			3304006.408	62	53290.426	

Here the CD4 counts were analyzed in these 3 groups of both LED microscopy and CBNAAT positivity, LED microscopy negative and CB NAAT positive and both the tests negative groups. Mean CD4 in both positive were 355.64 with ,In both negative group were 210.84 and LED microscopy negative and CBNAAT positive were 215.50.This also was found to be not statistically significant.

CONCLUSION

There was no statistically significant co relation with the CD4 count and methods of detecting tuberculosis in PLWHA when analyzed with Chi square and ANNOVA test using SPSS software.

CHAPTER- VI

CONCLUSION

1. The majority of Pulmonary tuberculosis suspects in HIV positive based on chest X ray and clinical findings were in a lower age group when compared to HIV negative patients when analyzed with chi square testing.
2. There is no statistically significant co relation between suspected PTB patients who are HIV positive and HIV negative based on sex distribution, when analyzed using Chi square test.
3. Mean BMI was 18.39 with a standard deviation of 2.35 among PTB suspecting HIV positive patients and it was 20.95 and 1.54 respectively in HIV negative patients. There was statistically significant co relation with the finding that the patients suspecting PTB among HIV negative individuals have a higher BMI than HIV positive, when analyzed using Chi square testing.
4. The increased detection of PTB with LED fluorescent microscopy in HIV negative patients when compared to HIV positive patients were statistically insignificant when Chi square test was applied using SPSS software.
5. :The increased detection of PTB with CBNAAT in HIV negative patients when compared to HIV positive patients were statistically insignificant when Chi square test was applied using SPSS software.

6. There was no statistically significant co relation in the detection of Rifampicin resistance by CBNAAT in PTB,HIV positive and negative groups when analysed with Chi square test,SPSS software
7. There was a better detection with CBNAAT when compared to fluorescent LED microscopy in ZN smear negative PTB in HIV positive patients. This was statistically significant when analysed with Chi square testing using SPSS software
8. There was no statistically significant co relation in HIV positive and HIV negative patients with the outcome of fluorescent LED microscopy and CBNAAT detection in suspected PTB, when analyzed with Chi square testing using SPSS software.

   This was in accordance with the studies conducted by Boheme et al.(5)
9. There was no statistically significant co relation in HIV positive and HIV negative patients with the detection of Tuberculous lymphadenitis with LED fluorescent microscopy, when analyzed with Chi square testing using SPSS software.
10. There was no statistically significant difference in HIV positive and HIV negative patients with the detection of tuberculous lymphadenitis with LED fluorescent microscopy, when analysed with Chi square testing using SPSS software.
11. There was no statistically significant difference between the detection of tuberculosis lymphadenitis using CB NAAT and fluorescent LED

microscopy among HIV positive patients. This was against the tests quoted. Probably because of low sample size.

12. There is statistically significant better detection with CBNAAT compared to LED microscopy, in patients who are HIV negative with tuberculous lymphadenitis.(13),analyzed with Chi square test,SPSS software
13. There is no statistically significant difference in detection of tuberculous pleural effusion with LED microscopy between HIV positive and negative patients, using Chi square test, SPSS software.
14. There is no statistically significant better detection of TB pleural effusion in HIV negative individuals, when compared to HIV positive, when analyzed with Chi square test, using SPSS software.
15. There is s statistically significant better detection with CB NAAT when compared to fluorescent LED microscopy in tuberculous pleural effusion in HIV positive patients.
16. There is s statistically significant better detection with CB NAAT when compared to fluorescent LED microscopy in tuberculous pleural effusion in HIV negative patients.
17. In Extra Pulmonary Tuberculosis, the results of two tests CBNAAT and LED fluorescence microscopy were not having statistically significant difference in HIV positive and negative patients when analysed with Chi square test, SPSS software.

18. There was no statistically significant co relation with the CD4 count and methods of detecting tuberculosis in PLWHA when analyzed with Chi square and ANNOVA test using SPSS software.

CHAPTER - VII

LIMITATIONS OF STUDY

1. Low sample size,(total 130,pulmonary tuberculosis-80, extra pulmonary tuberculosis-50)
2. Smaller duration of study (January 2015-April 2016)
3. Inadequate specimen varieties in extra pulmonary tuberculosis
4. Detection was not confirmed with the gold standard of detection, culture of Mycobacterium Tuberculosis
5. Rifampicin resistance not confirmed with line probe assay or culture
6. All the patients who were HIV negative were arbitrarily taken as having normal CD 4 count.

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PROFORMA

NAME :

AGE : ID NO :

WEIGHT : HEIGHT : BMI :

SEX :

HIV STATUS: POSITIVE/NEGATIVE

POSITIVE : ART /PRE ART

DURATION :

PULMONARY TB/EXTRA PULMONARY TB:

IF EXTRA PULMONARY : FNAC/PF

CXR FINDINGS : PRESENT/ABSENT

AFB POSITIVE/NEGATIVE

POSITIVE :

CBNAAT- HIGH / MEDIUM / LOW /VERY LOW

RIFAMPICIN RESISTANCE DETECTED / NOT DETECTED

CD4 COUNT :

நோயாளி ஒப்புதல் படிவம்

நான் _____ மகாத்மா காந்தி அரசு நினைவு மருத்துவமனையில் மாரடைப்புக்கு சிகிச்சை பெற்று வருகிறேன். இந்த மருத்தவமனையில் நடைபெறும் ஆய்வான "காசநோய் கண்டறிவதற்கான சிபி நாட் மற்றும் நுண் பரிசோதனை" செய்வதற்கு மருத்துவர் மூலம் எனது சொந்த மொழியில் அறிந்துகொண்டேன். இதில் பங்கேற்றுக்கொள்ள எனது சுயநினைவுடன் சம்மதம் அளிக்கிறேன்.

இடம் : கையொப்பம்

நாள் :

நோயாளி தகவல் தாள்

நோயாளியின் பெயர் :

வயது :

பாலினம் :

கல்வித் தகுதி :

வேலை :

நோயுற்ற காலம் :

நோயின் தன்மை :

உடனாளர் பெயர் :

உறவு :

உடனாளரின் கல்வித் தகுதி :

உடனாளரின் வேலை :

நான் _____ மகாத்மா காந்தி அரசு நினைவு மருத்துவமனையில் மாரடைப்புக்கு சிகிச்சை பெற்று வருகிறேன். இந்த மருத்தவமனையில் நடைபெறும் ஆய்வான "காசநோய் கண்டறிவதற்கான சிபி நாட் மற்றும் நுண் பரிசோதனை" பற்றி மருத்துவர் மூலம் எனது சொந்த மொழியில் அறிந்துகொண்டேன். இதில் பங்கேற்றுக்கொள்ள எனது சுயநினைவுடன் சம்மதம் அளிக்கிறேன்.

இடம் : கையொப்பம்

நாள் :

ETHICAL COMMITTEE CLEARANCE CERTIFICATE

K.A.P.VISWANATHAM GOVT. MEDICAL COLLEGE
TIRUCHIRAPALLI -1
INSTITUTIONAL ETHICS COMMITTEE

CERTIFICATE OF CLEARANCE

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Rtd. District Judge
Mrs.Kalavathy,
Exnora Social Worker, Trichy
Smt.S.Gayathri,
Lay person.

This is to certify that the project work titled DETECTION OF TUBERCULOSIS IN PLWHA, A STUDY OF YIELD BY CB-NAAT AND MICROSCOPY WITH CD4 CORRELATION proposed by Dr.K.Smitha Chandran, part of fulfillment of M.D/M.S course in the subject of General Medicine for the year 2014-2017 by The Tamilnadu Dr.MGR Medical University has been cleared by the Ethics committee.

8/12/17

CHAIRMAN,
Institutional Ethics Committee
K.A.P.Viswanatham Govt. Medical College, Tiruchirapalli -1

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CHAPTER-1

INTRODUCTION

MASTER CHART

NAME	AGE	SEX	WEIGHT	HEIGHT	BMI	HIV NEG	HIV POS ON ART/PRE ART	DURATION (MONTHS)	PULMONARY	EXTRA PULM TYPE	MICROSCOPY AFB	CBNAAT POSITIVE TYPE	RIFAMPICIN RESISTANCE	CD4 COUNT
PALANIYANDI	42	M	53	1.65	19.47	N	PRE ART	36	Y	NA	NEG	LOW	Not detect	442
DHILIPAN	27	M	50	1.6	19.53	N	PRE ART	1	Y	NA	NEG	VERY LOW	Not detect	276
HENDRY DOSS	46	M	70	1.7	24.22	N	PRE ART	1	Y	NA	NEG	LOW	Not detect	87
NANDINI	42	F	42	1.52	18.18	N	PRE ART	1	Y	NA	NEG	LOW	Not detect	63
LADHA	42	F	38	1.48	17.35	N	PRE ART	1	Y	NA	2+	HIGH	Not detect	39
SUBEDHA	60	F	26	1.38	13.65	N	PRE ART	1	Y	NA	NEG	LOW	Not detect	154
MANIVEL	43	M	55	1.68	19.49	N	PRE ART	1	Y	NA	NEG	VERY LOW	Not detect	128
NATARAJAN	56	M	43	1.7	14.88	N	PRE ART	1	Y	NA	1+	HIGH	Not detect	77
SESUMARY	36	F	47	1.56	19.31	N	PRE ART	1	Y	NA	NEG	VERY LOW	Not detect	223
PAPPA	39	F	44	1.56	18.08	N	PRE ART	1	Y	NA	NEG	NEG	NA	139
SUMATHI	45	F	33	1.43	16.14	N	PRE ART	1	Y	NA	1+	HIGH	Not detect	262
SEKAR	55	M	40	1.62	15.24	N	PRE ART	1	Y	NA	NEG	LOW	Not detect	112
NATARAJAN	65	M	50	1.69	17.51	N	PRE ART	1	Y	NA	1+	HIGH	Not detect	71
SARAVANAN	66	M	66	1.7	22.84	N	PRE ART	1	Y	NA	NEG	VERY LOW	Not detect	159
GUNASEKHARAN	47	M	56	1.68	19.84	N	PRE ART	1	Y	NA	1+	LOW	Not detect	178
BASKAR	43	M	55	1.67	19.72	N	PRE ART	1	Y	NA	1+	HIGH	Not detect	180
MEENA	33	F	34	1.47	15.73	N	PRE ART	1	Y	NA	NEG	NEG	NA	88
ELANGOVAN	41	M	48	1.6	18.75	N	PRE ART	1	Y	NA	NEG	NEG	NA	151
JESINTHA	32	F	37	1.48	16.89	N	PRE ART	1	Y	NA	NEG	NEG	NA	273
ASAITHAMBI	30	M	54	1.62	20.58	N	PRE ART	1	Y	NA	NEG	NEG	NA	190
SAKTHIVEL	28	M	55	1.68	19.49	N	PRE ART	84	Y	NA	NEG	NEG	NA	240
SELVAM	44	M	40	1.67	14.34	N	PRE ART	1	Y	NA	NEG	NEG	NA	63
SAVARIMUTHU	45	M	47	1.62	17.91	N	PRE ART	1	Y	NA	2+	MEDIUM	DETECTED	181
GOVINDARAJ	35	M	54	1.67	19.36	N	ART	72	Y	NA	NEG	NEG	NA	426
ANNALAKSHMI	35	F	40	1.5	17.78	N	ART	72	Y	NA	NEG	MEDIUM	Not detect	55
CHANDRASEKHAR	29	M	53	1.65	19.47	N	ART	36	Y	NA	NEG	HIGH	Not detect	131
MAHAMUNI	60	M	55	1.66	19.96	N	ART	48	Y	NA	NEG	VERY LOW	Not detect	302
CHANDRABALA	45	F	55	1.56	22.60	N	ART	48	Y	NA	1+	MEDIUM	Not detect	1224
SUMATHI	30	F	35	1.54	14.76	N	ART	48	Y	NA	NEG	LOW	Not detect	43
MURUGESAN	35	M	55	1.67	19.72	N	ART	48	Y	NA	NEG	NEG	NA	515
VETRIVEL	22	M	54	1.6	21.09	N	PRE ART	1	Y	NA	NEG	NEG	NA	490
BACKIYAM	60	F	46	1.5	20.44	N	PRE ART	1	Y	NA	NEG	NEG	NA	442
PASUPANDIYAN	17	M	54	1.6	21.09	N	PRE ART	1	Y	NA	NEG	NEG	NA	507
VEERAMANI	54	M	43	1.62	16.38	N	PRE ART	1	Y	NA	NEG	NEG	NA	40
KOLANJI	45	F	41	1.52	17.75	N	PRE ART	1	Y	NA	NEG	NEG	NA	98
VELMURUGAN	33	M	43	1.58	17.22	N	PRE ART	1	Y	NA	NEG	NEG	NA	106
VIJAYALAKSHMI	36	F	40	1.53	17.09	N	PRE ART	1	Y	NA	NEG	NEG	NA	120
JAYANTHI	39	F	39	1.54	16.44	N	PRE ART	1	Y	NA	NEG	NEG	NA	126
ARUMUGAM	48	M	48	1.65	17.63	N	PRE ART	1	Y	NA	NEG	NEG	NA	130
PONNUSAMY	41	M	46	1.58	18.43	N	PRE ART	1	N	FNAC	NEG	LOW	Not detect	220
MALATHY	28	F	48	1.5	21.33	N	PRE ART	1	N	FNAC	2+	LOW	Not detect	1029
MANIKANDAN	23	M	45	1.6	17.58	N	PRE ART	1	N	FNAC	1+	VERY LOW	Not detect	506
GOKILA	25	F	28	1.45	13.32	N	PRE ART	1	N	FNAC	NEG	LOW	Not detect	135
CHOKALINGHAM	35	M	65	1.68	23.03	N	PRE ART	1	N	FNAC	NEG	LOW	Not detect	225
KILLAMAN	18	M	47	1.55	19.56	N	PRE ART	72	N	FNAC	1+	LOW	Not detect	449
THOTTIYAN	46	F	43	1.5	19.11	N	PRE ART	72	N	FNAC	2+	MEDIUM	Not detect	335
SHOBANA	27	F	50	1.62	19.05	N	PRE ART	1	N	FNAC	NEG	LOW	Not detect	1143
NAGALAKSHMI	37	F	40	1.52	17.31	N	PRE ART	1	N	FNAC	NEG	MEDIUM	DETECTED	67

RAJIVAN	48	M	45	1.62	17.15	N	PRE ART	1	N	FNAC	NEG	LOW	NA	215
SUMATHI	30	F	47	1.54	19.82	N	PRE ART	1	N	FNAC	NEG	NEG	NA	156
GOPI	45	M	55	1.58	22.03	N	PRE ART	1	N	PF	NEG	NEG	NA	345
MANIKANDAN	62	M	62	1.64	23.05	N	PRE ART	1	N	PF	NEG	NEG	NA	278
KISHAN	30	M	46	1.48	21.00	N	PRE ART	1	N	PF	NEG	NEG	NA	222
PRIYA	16	F	20	1.5	8.89	N	PRE ART	1	N	PF	1+	HIGH	Not detect	98
GOVINDAN	60	M	40	1.57	16.23	N	ART	36	N	PF	NEG	LOW	Not detect	130
SANKARI	42	F	45	1.53	19.22	N	PRE ART	1	N	PF	NEG	NEG	NA	142
SELVI	43	F	42	1.54	17.71	N	PRE ART	1	N	PF	NEG	NEG	NA	148
RAJAGOPAL	52	M	49	1.55	20.40	N	PRE ART	1	N	PF	NEG	NEG	NA	156
PRAKASHAM	50	M	46	1.56	18.90	N	PRE ART	1	N	PF	NEG	NEG	Not detect	160
BALAKRISHNAN	45	M	50	1.65	18.37	N	ART	72	N	PF	NEG	NEG	NA	130
Deivigam	58	M	52	1.64	19.33372992	Y	NA	NA	Y	NA	NEG	MTB High	Not detect	>750
Rajendran	32	M	60	1.7	20.76124567	Y	NA	NA	Y	NA	NEG	MTB VLow	Not detect	>750
Vadivel	37	M	57	1.69	19.95728441	Y	NA	NA	Y	NA	NEG	MTB Medium	Not detect	>750
sundaramoorthi	36	M	59	1.75	19.26530612	Y	NA	NA	Y	NA	NEG	MTB Medium	Not detect	>750
Muthaiyan	61	M	51	1.62	19.43301326	Y	NA	NA	Y	NA	NEG	MTB Low	Not detect	>750
Laxmi narasimman	58	M	53	1.64	19.70553242	Y	NA	NA	Y	NA	2+	MTB High	Detected	>750
Sebastin	65	M	54	1.68	19.13265306	Y	NA	NA	Y	NA	NEG	MTB Low	Not detect	>750
Devendran	38	M	50	1.63	18.81892431	Y	NA	NA	Y	NA	3+	MTB High	Detected	>750
Mohamed sarif	18	M	51	1.63	19.1953028	Y	NA	NA	Y	NA	NEG	MTB Low	Not detect	>750
Sumathi	50	F	54	1.65	19.83471074	Y	NA	NA	Y	NA	1+	MTB Medium	Not detect	>750
Ramalingam	42	M	61	1.74	20.14797199	Y	NA	NA	Y	NA	NEG	MTB VLow	Not detect	>750
Hemalatha	13	F	55	1.67	19.72103697	Y	NA	NA	Y	NA	3+	MTB High	Not detect	>750
Selvam	60	M	53	1.63	19.94805977	Y	NA	NA	Y	NA	NEG	MTB Low	Not detect	>750
Manikandan	20	M	52	1.65	19.10009183	Y	NA	NA	Y	NA	NEG	MTB Medium	Not detect	>750
Raju	59	M	60	1.74	19.81767737	Y	NA	NA	Y	NA	3+	MTB High	Not detect	>750
Kaliyammal	50	F	51	1.6	19.921875	Y	NA	NA	Y	NA	NEG	MTB Low	Not detect	>750
Balan	38	M	53	1.65	19.46740129	Y	NA	NA	Y	NA	NEG	MTB VLow	Not detect	>750
Paramasivam	55	M	51	1.61	19.67516685	Y	NA	NA	Y	NA	2+	MTB Medium	Not detect	>750
Gomathy	40	F	59	1.72	19.94321255	Y	NA	NA	Y	NA	NEG	MTB Low	Not detect	>750
Gayathri	14	F	56	1.68	19.84126984	Y	NA	NA	Y	NA	NEG	MTB VLow	Not detect	>750
Ajithkumar	18	M	52	1.63	19.57168128	Y	NA	NA	Y	NA	NEG	MTB Low	Not detect	>750
Nishandhini	6	F	55	1.58	22.03	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Murugesan	39	M	62	1.64	23.05	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Thenmozhi	58	F	55	1.56	22.60	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Mathan	7	M	58	1.65	21.30	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Dhanam	30	F	59	1.6	23.05	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Chokkalingam	50	M	70	1.7	24.22	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Thamas	31	M	49	1.52	21.21	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Sesuraj	63	M	51	1.48	23.28	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
M.Maruthairaj	62	M	52	1.45	24.73	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Rajeshbaskar	5	M	57	1.58	22.83	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Balasubramaniyam	30	M	62	1.64	23.05	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Arumugam	80	M	55	1.56	22.60	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Ladha	52	F	60	1.65	22.04	Y	NA	NA	Y	NA	NEG	NEG	NA	>750
Chinnaiya	44	M	32	1.4	16.33	Y	NA	NA	N	FNAC	2+	MTB High	Not detect	>750
Surendar	20	M	35	1.5	15.56	Y	NA	NA	N	FNAC	1+	MTB Low	Not detect	>750
Chinaiyan	44	M	42	1.6	16.41	Y	NA	NA	N	FNAC	1+	MTB Medium	Not detect	>750
Chinnaya	44	M	47	1.64	17.47	Y	NA	NA	N	FNAC	3+	MTB High	Not detect	>750
Amutha	50	F	47	1.64	17.47	Y	NA	NA	N	FNAC	NEG	MTB VLow	Not detect	>750
Sathyapriya	13	F	26	1.3	15.38	Y	NA	NA	N	FNAC	1+	MTB Medium	Not detect	>750
Nivetha	14	F	28	1.32	16.07	Y	NA	NA	N	FNAC	NEG	MTB Low	Not detect	>750
Raja	40	M	46	1.5	20.44	Y	NA	NA	N	FNAC	NEG	NEG	NA	>750
Hasina begam	26	F	49	1.56	20.13	Y	NA	NA	N	FNAC	NEG	NEG	NA	>750

Kalaimathi	27	F	52	1.66	18.87	Y	NA	NA	N	FNAC	1+	MTB Low	Not detect	>750
Kathiresan	44	M	59	1.65	21.67	Y	NA	NA	N	FNAC	NEG	NEG	NA	>750
Murugan	67	M	62	1.56	25.48	Y	NA	NA	N	FNAC	NEG	NEG	NA	>750
velayuthan	40	M	56	1.6	21.88	Y	NA	NA	N	FNAC	NEG	NEG	NA	>750
Kavitha	34	F	58	1.56	23.83	Y	NA	NA	N	FNAC	NEG	NEG	NA	>750
Vijayarani	23	F	38	1.68	13.46	Y	NA	NA	N	FNAC	1+	MTB Medium	Not detect	>750
Immanvel	13	M	34	1.3	20.12	Y	NA	NA	N	PF	1+	LOW	NA	>750
Thayammal	40	F	54	1.6	21.09	Y	NA	NA	N	PF	1+	LOW	NA	>750
Kaliyammal	60	F	52	1.4	26.53	Y	NA	NA	N	PF	NEG	LOW	NA	>750
Vijayalakshmi	37	F	56	1.65	20.57	Y	NA	NA	N	PF	NEG	NEG	NA	>750
Baskar	25	M	57	1.56	23.42	Y	NA	NA	N	PF	NEG	NEG	NA	>750
Velu	78	M	54	1.64	20.08	Y	NA	NA	N	PF	NEG	NEG	NA	>750
Parayandi	53	M	43	1.43	21.03	Y	NA	NA	N	PF	NEG	NEG	NA	>750
Krishnan	35	M	70	1.65	25.71	Y	NA	NA	N	PF	NEG	NEG	NA	>750
Kanagavalli	22	F	47	1.4	23.98	Y	NA	NA	N	PF	NEG	NEG	NA	>750
Raja	35	M	46	1.49	20.72	Y	NA	NA	N	PF	NEG	NEG	NA	>750
ganapathy	48	M	48	1.65	17.63	N	PRE ART	1	Y	NA	NEG	NEG	NA	130
CHELLAMMAL	60	F	45	1.53	19.22337562	Y		NA	Y	NA	NEG	MTB Low	Not detect	>750
Muthuveeran	30	M	63	1.65	23.14	Y	NA	NA	Y	NA	2+	MTB Low	Not detect	>750
Roslin	31	F	54	1.54	22.77	Y	NA	NA	Y	NA	1+	MTB Low	Not detect	>750
Palanikumar	18	M	45	1.65	16.53	Y	NA	NA	Y	NA	NEG	MTB Low	Not detect	>750
Catherine asha	25	F	45	1.54	18.97	Y	NA	NA	Y	NA	1+	MTB Low	Not detect	>750
MONISHA	19	F	34	1.4	17.34693878	Y	NA	NA	Y	NA	NEG	MEDIUM	Not detect	>750

ABBREVIATIONS

AFB	:	ACID FAST BACILLI
AIDS	:	ACQUIRED IMMUNO DEFECIENCY SYNDROME
ART	:	ANTI RETRO VIRAL THERAPY
ATT	:	ANTI TUBERCULOUS THERAPY
BMI	:	BODY MASS INDEX
CBNAAT	:	CATRIDGE BASED NUCLEIC ACID AMPLIFICATION TEST
CD 4	:	CLUSTER OF DIFFERENTIATION
CFU	:	COLONY FORMING UNIT
CMI	:	CELL MEDIATED IMMUNITY
CNS	:	CENTRAL NERVOUS SYSTEM
CT	:	COMPUTERISED TOMOGRAPHY
EPTB	:	EXTRA PULMONARY TUBERCULOSIS
FNAC	:	FINE NEEDLE ASPIRATION CYTOLOGY
HIV	:	HUMAN IMMUNO DEFICIENCY VIRUS
IL	:	INTERLEUKIN
INH	:	ISONIAZID
LED	:	LIGHT EMITTING DIODE
MDR	:	MULTI DRUG RESISTANT
MRI	:	MAGNETIC RESONANCE IMAGING
MTB	:	MYCOBACTERIUM TUBERCULOSIS

MTB/RIF	:	MYCOBACTERIUM TUBERCULOSIS/RIFAMPICIN RESISTANCE
PA view	:	POSTERO ANTERIOR
PLWHA	:	PERSONS LIVING WITH HIV AND AIDS
PTB	:	PULMONARY TUBERCULOSIS
RIF	:	RIFAMPICIN
RNTCP	:	REVISED NATIONAL TUBERCULOSIS CONTROL PROGRAM
rpoB	:	RNA POLYMERASE B
SPSS	:	STATISTICAL PRACTICE IN SOCIAL SCIENCES
TB	:	TUBERCULOSIS
TH 1	:	T HELPER CELLS
TNF	:	TUMOUR NECROSIS FACTOR
TST	:	TUBERCULIN SENSITIVITY TEST
XDR TB	:	XTREMELY DRUG RESISTANT TUBERCULOSIS
ZN	:	ZEIHL NEELSON